AN-Najah National University

Faculty of Graduate Studies

Synthesis and Modeling of Water Soluble Mixed Triamine/Diamine/Copper (II) Complexes and their Antibacterial Activities

By

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Dedication

I dedicate my thesis:

To my beloved parents Ali, Wafaa Abu Saleema, to my husband Morad Aqtash and my son zain.

To my dear brothers and sisters Mohammad, Tariq, Haya, Sama, ghadeer. To my special friend Manar

To all of my friends.

To my doctors at the An-Najah National University –Nablus.

To all people and Muslims in the world.

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First of all, I thank Almighty Allah for giving me the strength and the patience that I needed to stay on the path of learning and finish my thesis.

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Also, I would like to thank Dr. Paula Brandao, and thank to KSU University for TGA measurements.

الاقرار

أنا الموقع أدناه مقدم الرسالة التي تحمل العنوان :

Synthesis and Modeling of Water Soluble Mixed Triamine/ Diamine/Copper (II) Complexes and their Antibacterial Activities

أقر بأن ما اشتملت عليه هذه الرسالة انما هو نتاج جهدي الخاص باستثناء ما تمت الاشارة اليه حيثما ورد وان هذه الرسالة ككل او جزء منها لم يقدم من قبل لنيل أي درجة علمية أو بحث علمي أو بحثي لدى أي مؤسسة تعليمية أو بحثية.

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The work provided in this thesis, unless otherwise referenced, is the researcher's own work, and has not been submitted elsewhere for any other degree or qualification.

Student Name: **اسم الطالب:**

Signature: **التوقيع:**

Date: **التاريخ:**

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Abbreviations

Symbol	Structure/Name
TGA	Thermogravimetric analysis
DNA	Deoxyribonucleic acid
dien	Diethylenetriamine
DETA	Diethylenetriamine
CHN	Elemental analysis
CCDC NO. 1437266	Cambridge Crystallographic Data Centre
dipn	3,3-Diamino propyl-amine
Me_4en	Tetra methyl ethylene diamine
DMSO	Dimethyl sulfoxide
EtOH	Ethanol
DMF	Dimethylformamide
DTA	Differential thermal analysis
$TBAPF_6$	Tetrabutylammonium hexafluorophosphate
MIC	Minimum inhibitory concentration
MBC	Minimum bacteriocidal concentration

Synthesis and Modeling of Water Soluble Mixed Triamine/Diamine/Copper (II) Complexes and their Antibacterial Activities

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Abstract

Triamine and diamine ligands were mixed to prepare several copper(II) complexes of general formula [Cu(dien)NN]X_2**.** [dien = diethelenetriamine and NN is diamines like: *en* = ethylenediamine or Me_4en = N,N′,N,N′-tetramethylethylenediamine (**1-14**) and X : is Br or Cl] under ultrasonic mode with a relatively high yield. These complexes were characterized by elemental microanalysis, UV visible IR spectroscopy, thermal and electrochemical techniques. In addition, complex **7** structure was solved by X-ray single crystal and treated with Hirshfeld surface analysis. This complex exhibited a distorted square pyramidal coordination environment around Cu(II) centre. The solvatochromism of the desired complexes was investigated in water and other suitable organic solvents. The results showed that the Guttmann's DN parameter values of the solvents have mainly contributed to the shift of the d–d absorption band towards the linear increase in the wavelength of the absorption maxima of the complexes. Most of the complexes showed higher antibacterial activity against the studied microorganisms than other.

Background

Copper is an essential element that plays an important role in human bodies. This element, along with amino and fatty acids as well as vitamins, is required for normal metabolic processes. However, copper can't be synthesized in bodies; the human diet must supply regular amounts of it for absorption [1].

Copper is found in nature as a pure metal, and this was the source of the first metal to be used by humans.

Copper is fundamental to all organisms, because it is a key constituent of the respiratory enzyme complex cytochrome oxidase. Liver, bone and muscle are the main region where copper is found in humans. Copper compounds are used as wood preservatives, fungicides, and bacteriostatic substances [2].

In biological application, Amine-Copper (II) complexes exhibit prominent antimicrobial and anticancer potential activity by inducing apoptosis. In general, redox-active agents that damage DNA in vitro are thought to exhibit apoptotic activities in live cells by inducing oxidative stress and/or DNA damage [3].

Why Copper?

Copper, a bio-essential element, plays an important role in biological processes that involve electron transfer reactions, in fact copper (II) complexes with O, N, and S have been widely studied and they are proved to be good anticancer agents due to their strong binding affinity with DNA [4-6].

It has been demonstrated that copper assembles in tumors due to the selective permeability of cancer cell membranes to copper compounds [4-5].

Copper is a very important metal in life, photosynthesis process, mitochondrial respiratory, carbon and nitrogen metabolism, and oxidative stress protection [6].

Copper (II) is very cheap and available in the general lab, in addition copper complex revealed good stability.

Copper as a Catalyst:

These catalysts are important tools in industrial applications, including partial oxidation of methanol, synthesis of methanol and other derived fuels from CO_2, and production of hydrogen. A better understanding of them could pave the way for better catalyst designs .Copper-based catalysts are widely used in chemical industries to convert water and carbon monoxide to hydrogen, carbon dioxide, and methanol. As in equation 1 [7].

$$H_2O + CO \xrightarrow{\text{Cu (cat)}} H_2 + CO_2 + CH_3OH \quad (1)$$

There are theoretical models used to explain this reaction, but a complete understanding of the process is still unknown. However, recent research at the ALS has shed light on the process, giving scientists key data about how copper-based catalysts function at the atomic level.

Copper as Antibacterial Agent:

Copper complexes and CuO Nanoparticles, play a versatile role in antibacterial activities, several Cu complexes were evaluated as against Gram-positive and Gram negative bacterial. copper surfaces that affect bacteria in two sequential steps: the first step is a direct interaction between

the surface and the bacterial outer membrane, causing the membrane to rupture. The second is related to the holes in the outer membrane, through which the cell loses vital nutrients and water, causing a general weakening of the cell [8].

Copper as Antifungal Agent:

Schiff base polydentate ligands and their Copper(II) complexes showed a lot of antifungal activities against various types of fungi such, Rhizopusstolonifer, Rhizoctoniabataticola, Candida albicans, Aspergillus Niger, and, Aspergillus flavus [12].

Copper as Antitumor and Anticancer

It has been established that the properties of copper-coordinated compounds are largely determined by the nature of ligands and donor atoms bound to the metal ion. In this thesis, the most remarkable achievements in the design and development of copper (I, II) complexes as antitumor agents are discussed. Special emphasis has been focused on the identification of structure-activity relationships for different classes of copper (I, II) complexes. This work was motivated by the observation that no comprehensive surveys of copper complexes as anticancer agents were available in the literature. Moreover, up to now, despite the enormous efforts in synthesizing different classes of copper complexes, very few data concerning the molecular basis of the mechanisms underlying their antitumor activity are available. This overview, collecting the most significant strategies adopted in the last ten years to design promising anticancer copper(I,II) compounds, which would be a help to the researchers working in this field[9].

Chapter One

Introduction

1. Introduction

The synthesis of polyamino-Cu (II) complexes is important parts of research, due to their biomedical and catalysis applications [10-17]. Mixed-ligand copper(II) complexes with poly-nitrogen donors were investigated in a pharmaceutical field, due to their anticancer, antioxidant and antimicrobial potentials [15-22].

Copper (II) complexes were possessing antimicrobial and anti-tumour capability through inducing apoptosis. Indeed, they show activity both in vitro and in vivo, strongly binding and cleaving DNA [21-25]. In general, redox-active agents [26] one of that causes DNA damage and/or oxidative stress.

The study of solvatochromic behavior of complexes is very important since, it provides a quantitative access to recognize the solvent behavior and the role of the solvent in sphere coordination [27]. The solvatochromism phenomena in metal complexes are mainly divided into two types; direct and indirect faction attachments of the solvent molecules onto metal ion center in the complexes [28-29].

Diethylenetriamine (dien) and their derivative ligands with tridentate N-donor ligands are suitably placed to form two 5-member-chelate-metal complexes.

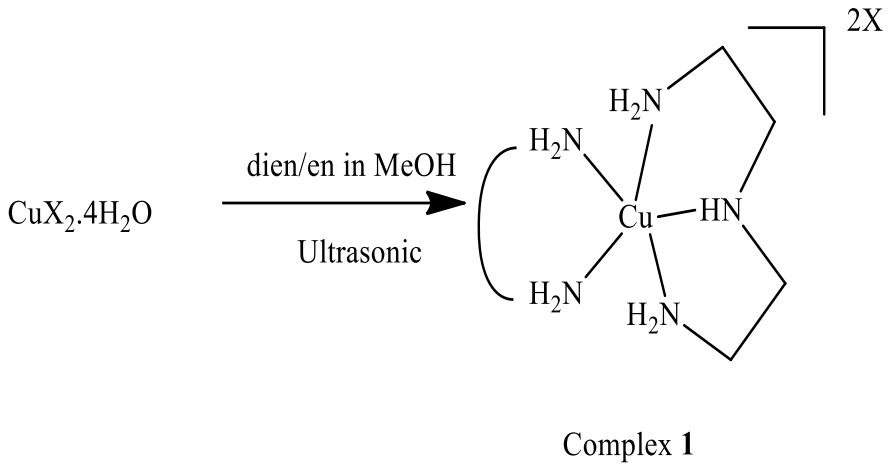
Although these complexes, with such tridentate amine ligands, have been thoroughly investigated, only one example which combines both bidentate and tridentate amine for preparation of mononuclear [Cu(II)/triamine/ diamine] X_2 complexes, have been isolated and characterized by X-ray single

crystal diffraction up to date . The authors have recently investigated the spectroscopic and the biological activity of [Cu(dien)(N-N)]X_2 [dien = dipropylenetriamine, *NN*: *en* = ethylenediamine or 2,2-dimethyl-1,3-propanediamin or 1-(2-aminoethyl) or 1,3-diaminopropane or 1,2-diaminocyclohexane or 1,2-diaminopropane or *Me_4en* = and *N,N,N,N* tetramethylethylenediamine] [22]. The structure of [Cu(dipn)(pn)]Br_2 was resolved by X-ray single crystal analysis. Herein, it is reported that the synthesis, solvatochromism and the spectroscopic properties of two new dicationic copper (II) complexes of general formula [Cu (dien) (diamine)]X_2 through simple and high yield procedure. Spectral, thermal and electrochemical analyses were investigated to identify the desired complexes. The structures of complex **(10-14)** were confirmed by the X-ray single crystal diffraction combined with Hirshfeld surface analysis.

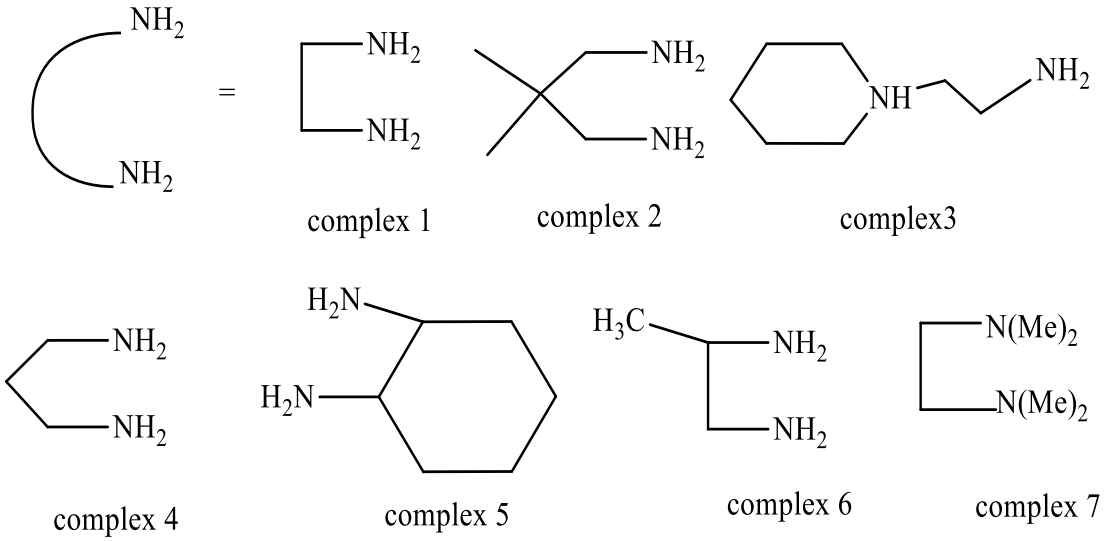
Chapter Two
Results and Discussion

Result and Discussion

Ultrasonic waves were applied to increase solubility and accelerate the synthesis of mixed diamine/triamine copper (II) complexes of the general formula [Cu (DETA) (N_2)]X_2 **(10-11)** in excellent yields. A blue colour was obtained which was visible by eye, when amines (N-donor ligands) were coordinated to the center. The displacement of internal coordination sphere bromide ionic ligands from $CuBr_2$ by dien and en ligands to the outer sphere as shown in **Scheme 1** was carried out very fast in one part of ultrasonic radiation mode reaction. Carrying out the reaction without use of ultrasonic radiation decreased the rate of reaction and revealed unwanted oily side products. The 3D chemical structures of the synthesized complexes were distinguished by using spectral methods and CHN analysis. These complexes were separated in dication halide salt which is due to conductivity and water solubility. The X-ray single crystal structure of **2** supports such suggestion and shows the geometry of Cu (II) dication in distorted square pyramidal form.



Complex **1**



Scheme 1 Synthesis of Complexes **1-7** (bromide), and Complexes 8-14 (chloride).

X = Br, Cl, complex 1 = (1-Br, 1- Cl).

1. Crystal structure for complex 7·H_2O

Complex **7** –crystallized in the monoclinic with $P2_1/n$ space group. Selected bond distances and angles are listed in Table 2. The crystal structure of [Cu (dien)Me_4en]Br_2 ·H_2O (**2**) is built up from an asymmetric unit composed of one Cu (dien)Me_4en)$^{2+}$ cation and two Br^-counter ions

and one crystallization water molecule. The asymmetric unit of complex **7** shown in Figure **1**, with the adopted labelling scheme, shows the nitrogen diamine and triamine atoms protonated as revealed by the last difference Fourier maps that are calculated along the structure refinement. All data are deposited with CCDC No. 1437266.

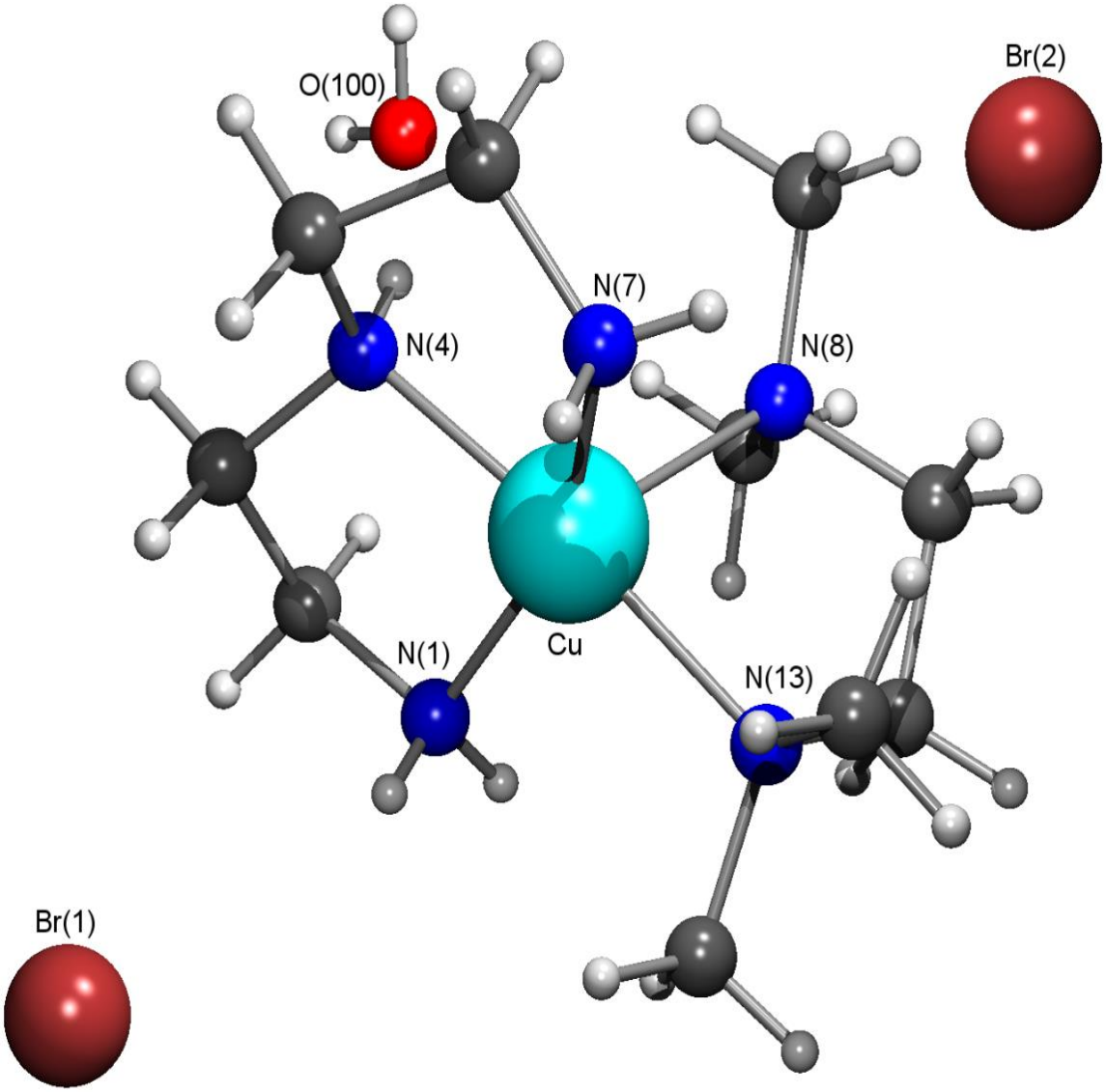


Figure 1. Asymmetric unit of complex 7 ·H_2O and the relation to adopted atomic labelling scheme.

Geometry coordination around copper center can be described as a square pyramid distorted towards a trigonal bipyramidal arrangement by a τ value of 0.32º. This trigonal index was calculated using the formula τ = (β-α)/60 previously defined by Addison *et al* [28], with τ assuming the values of 0 or 1 for ideal square-pyramidal and trigonal bipyramidal geometries, respectively. In complex **2** β and α correspond to N(4)-Cu-N(13) and to N(1)-Cu-N(7) angles, respectively. The equatorial coordination of copper center is composed of four nitrogen atoms from diethelenetriamine (N1, N4 and N7) and N,N,N,N-tetramethyletheylendiamine (N13). The N(8) occupies the apical pyramidal position at 2.161(3) Å from the copper center. These Cu-N distances ranging from 2.0246(19) to 2.2873(17) Å, are within the expected values of the copper(II) complexes with these type of amine ligands [29].

The structural features of the present compounds are very similar to what was reported by the authors [Cu (dipn) (N-N)] Br_2 [22, 27].

Table 1.Selected bond distances and angles of [Cu (dien) Me4en] Br2 ·H_2O (2)

Bond lenghts / Å			
Cu-N(1)	2.0452(19)	Cu-N(8)	2.2873(17)
Cu-N(4)	2.0246(19)	Cu-N(13)	2.0929(17)
Cu-N(7)	2.0354(19)		
Bond angles / º			
N(1)-Cu-N(4)	82.91(8)	N(4)- Cu-N(8)	102.35(8)
N(1)- Cu-N(7)	154.17(8)	N(4)- Cu-N(13)	173.60(8)
N(1)- Cu-N(8)	105.55(8)	N(7)- Cu-N(8)	98.47(7)
N(1)- Cu-N(13)	94.61(8)	N(7)- Cu-N(13)	97.25(7)
N(4)- Cu-N(7)	82.81(8)	N(8)- Cu-N(13)	83.99(6)

The N···O, N···Br and O···Br intermolecular distances found in the crystalline lattice are consistent with the existence of a 3-D dimensional network (see Figure 2) of N–H···O, N–H···Br and O–H···Br hydrogen bonding interactions between $[Cu(dien)Me_4en]^{2+}$cations, water crystallization molecule and Br^- anions, with N···Brand O···Br distances ranging from 3.256(3) to 3.561(3) Å, and a single N–H···O hydrogen bond with a N···O distance of 2.904(4) Å.

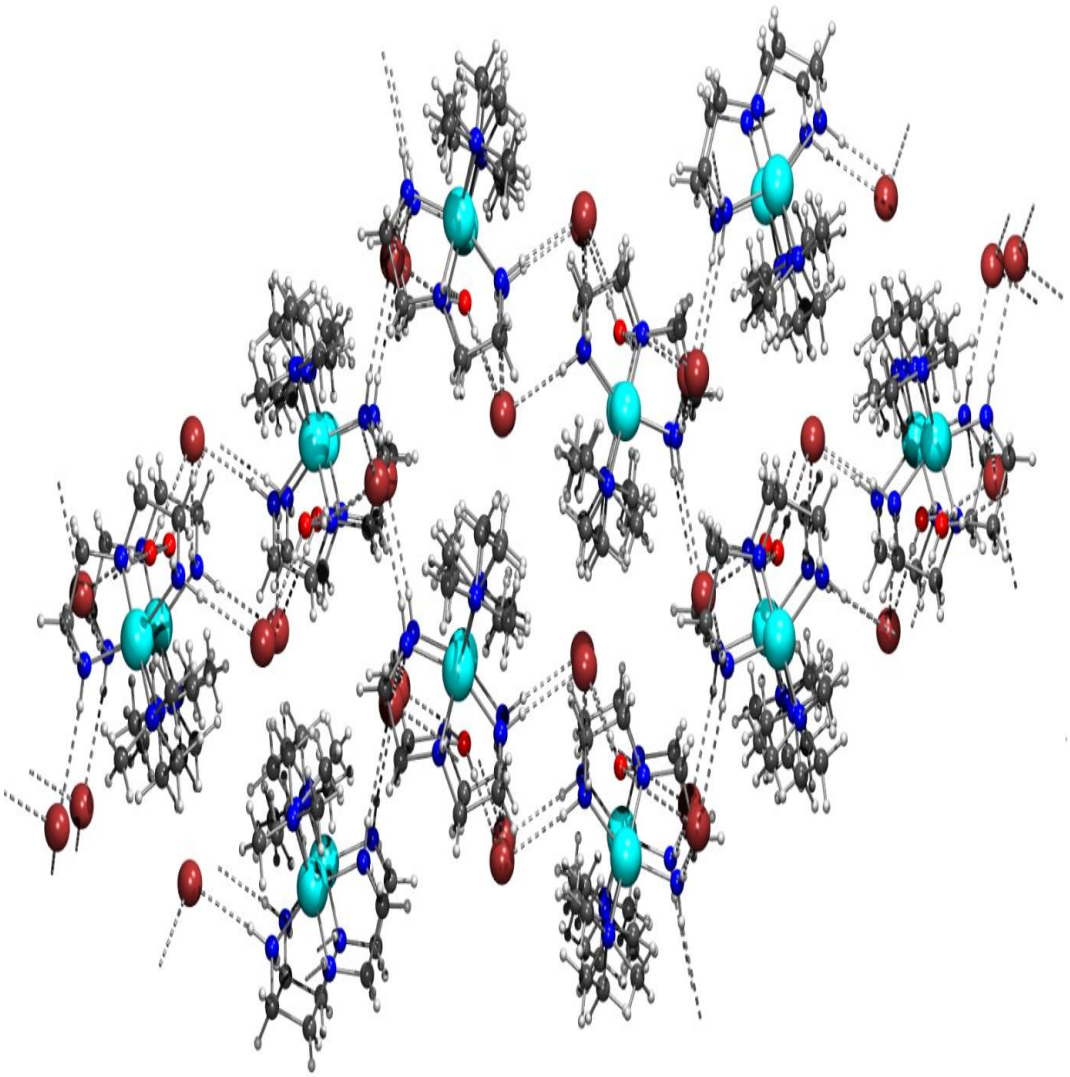


Figure 2. Crystal packing diagram of complex **2** along the *a-axis*. The hydrogen bonds are drawn in grey dashed lines

2. Hirshfeld surface analysis for complex 7

The Hirshfeld surface of complex **7** is shown in **Figure 3**. The red spotnjs over the surface indicate the inter-contacts involved in hydrogen bond [11, 39]. The dark-red spots on the d_{norm} surface rise as a result of the short interatomic contacts, i.e., strong hydrogen bonds, while the other intermolecular interactions appear in light-red spots.

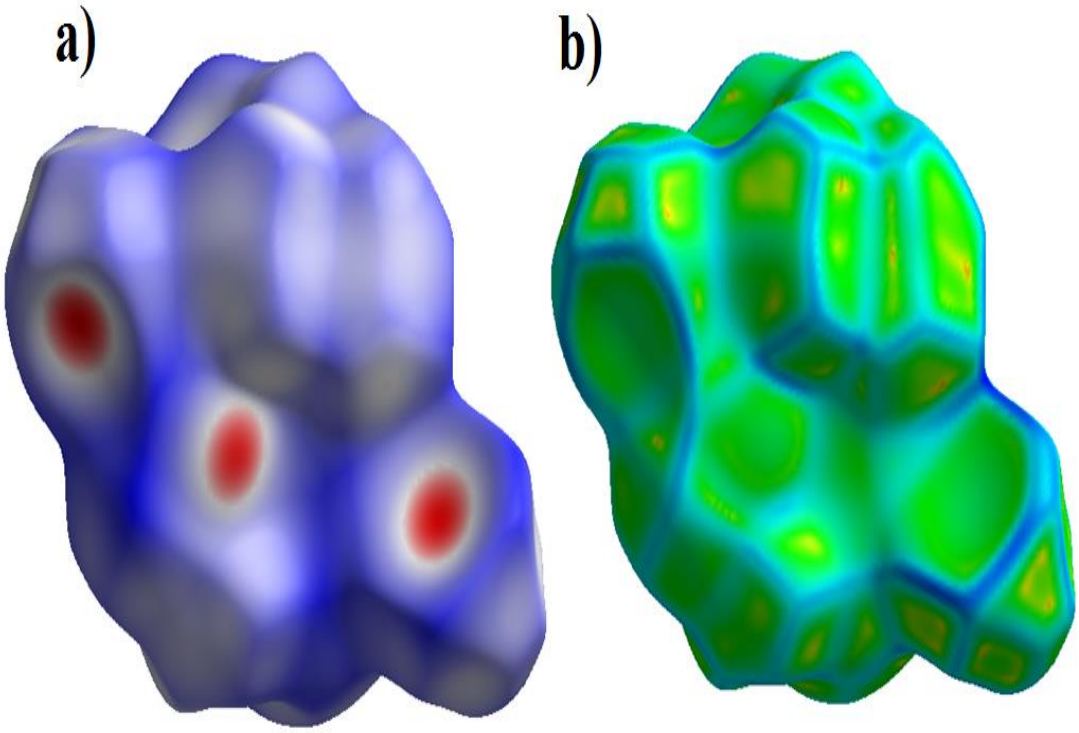


Figure 3. d_{norm} mapped a) and curedness b) on Hirshfeld surface for visualizing the inter-contacts of complex **7**. Colour scale ranges between − 0.18 au (blue) to 1.4 au (red).

The 2D Fingerprint plots over the Hirshfeld surfaces show the presence of inter-contacts H…H (64.6 %), H…Br (34.4 %) and H…Cu (1.0 %) (Figure 4). The major contribution is from H…H, while the least contribution is from H…Cu.

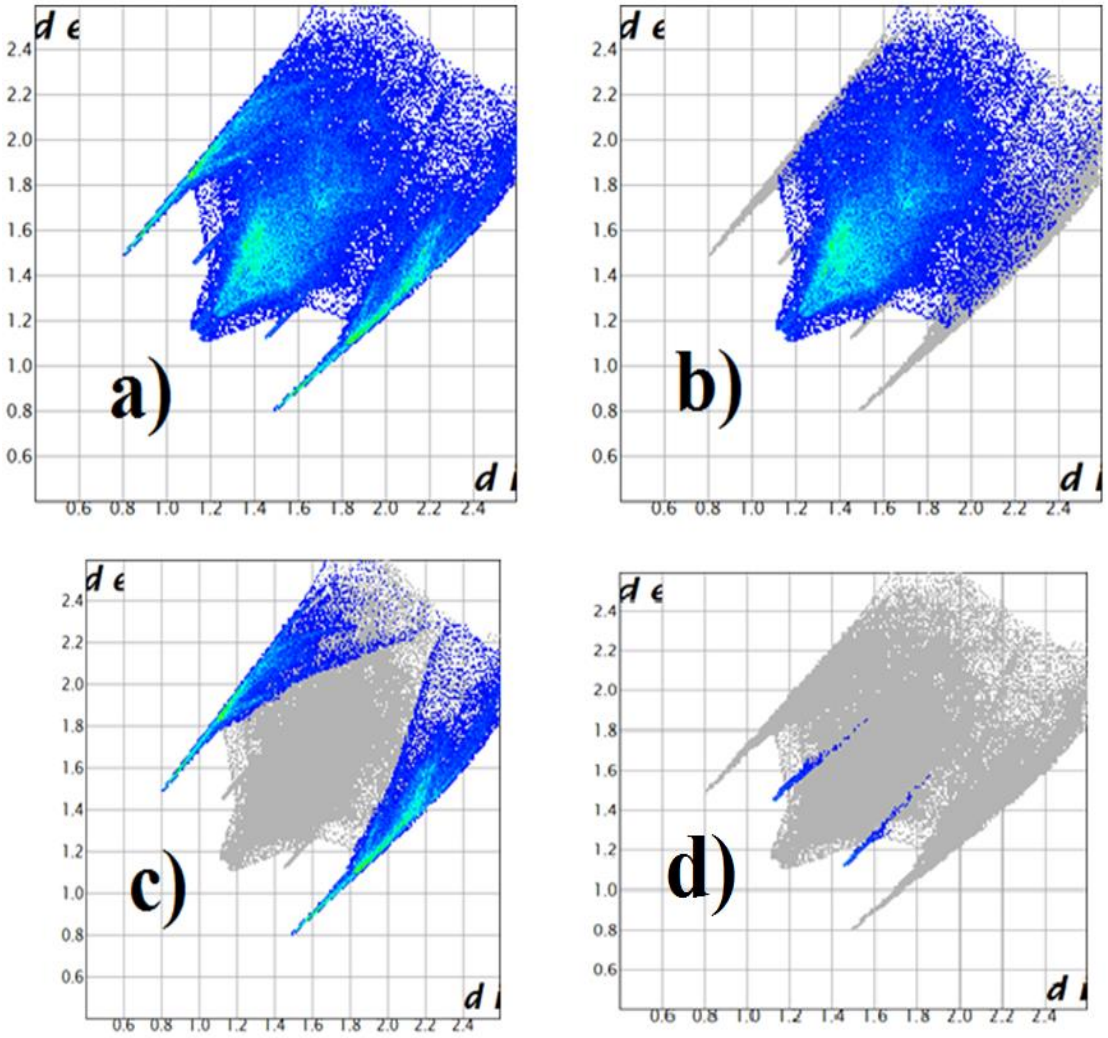


Figure 4. Fingerprint of complex **7**, (a) H...all (b) H...H, (c) H...Br and (d) H...Cu.

"The outline of the full fingerprint is shown in grey. *di* is the closest internal distance from a given point on the Hirshfeld surface and *de* is the closest external contacts" [40, 41].

3. UV-Vis measurements for the complexes

A sample of the target complexes in dist. H_2O was used to study the electronic absorption spectra behaviours at room temperature. The complexes have similar UV-visible behaviour. In the UV region, a high intense π to π* electron transitions around 250 nm (for complex **1**) and 255

nm (for complex **7**) respectively, while around 610 nm (for complex **1**) and 625 nm (for complex **7**), a low intensity d to d electron transitions band was recorded as shown in **Figure 5**.

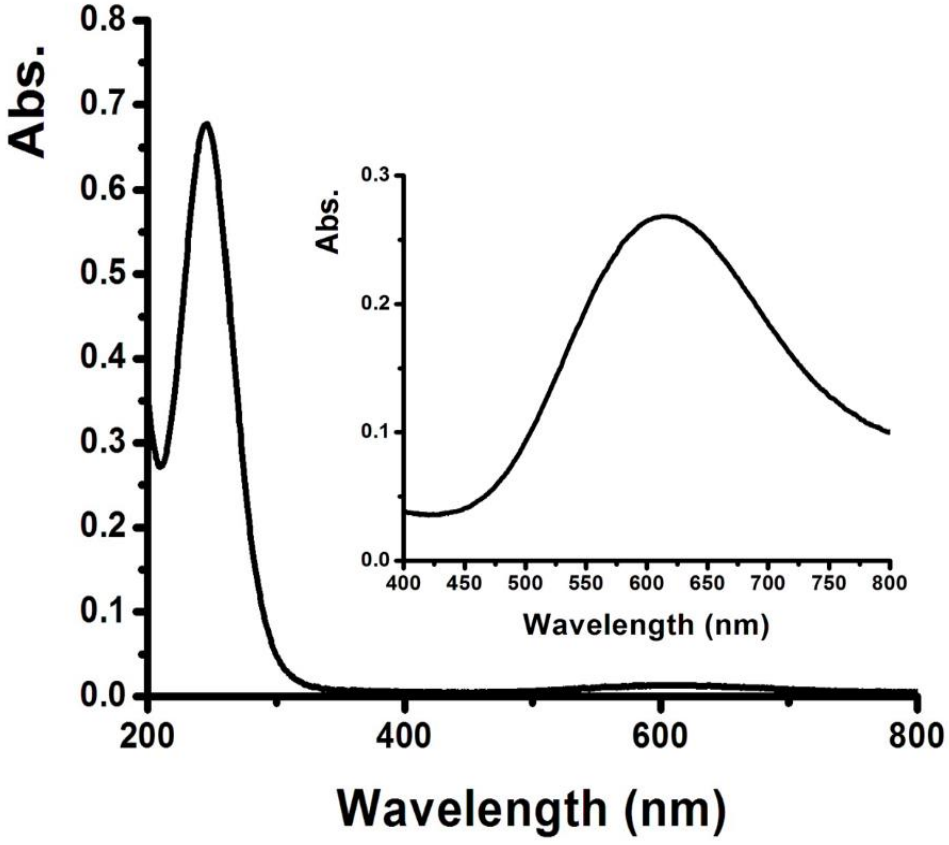


Figure 5. Electronic Spectrum of Complex **7** in Dist. H_2O

Interestingly, by subjecting the same complex **7** to UV-visible at room temperature using DMSO solvent, as shown in **Figure 6**. d to d electron transition bands became broader with bathochromic shift to ~ 700 nm maxima. A new sharp band at ~ 310 nm was recorded as metal-to-ligand charge-transfer (MLCT), the

π-π* electron transition bands have not changed. This observation may be due to the solvatochromic replacement of water molecule from the complex structure by the DMSO molecule.

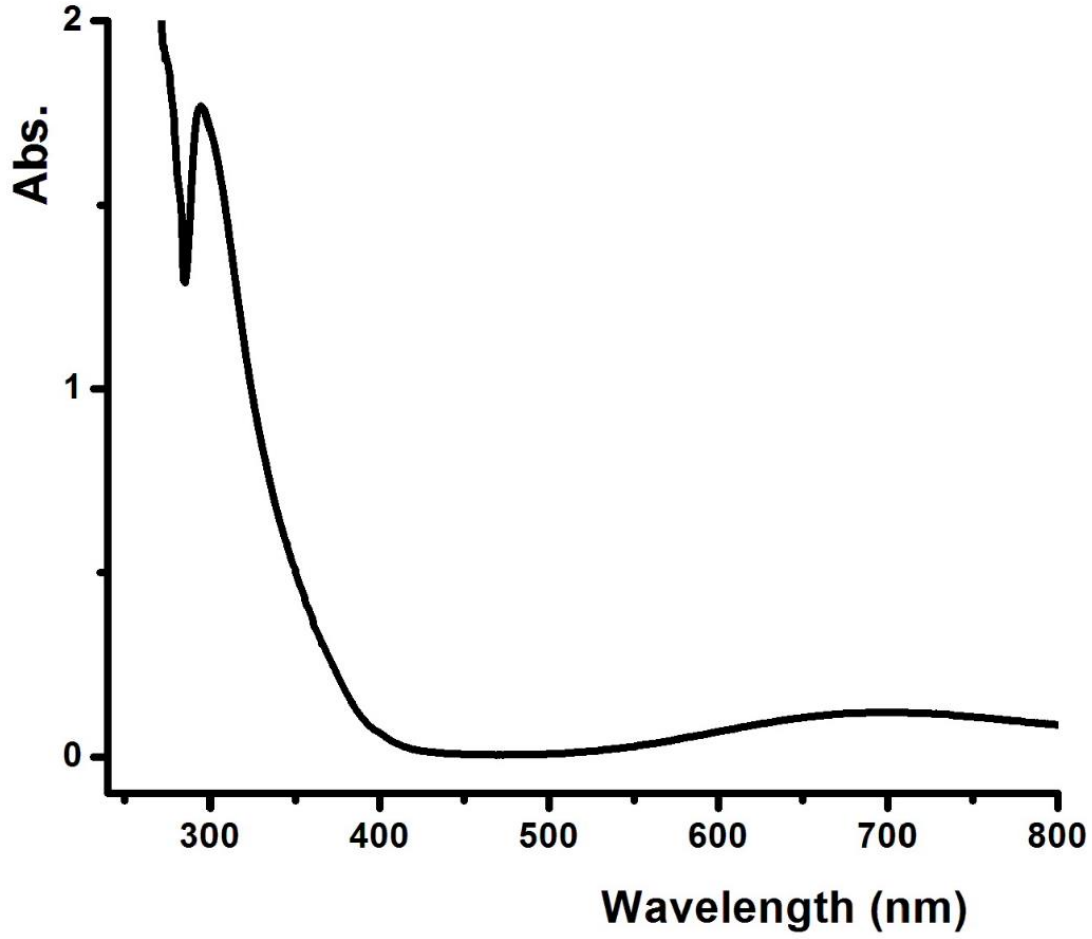


Figure 6. UV–Vis spectrum of **Complex 7** dissolved in DMSO at room temperature.

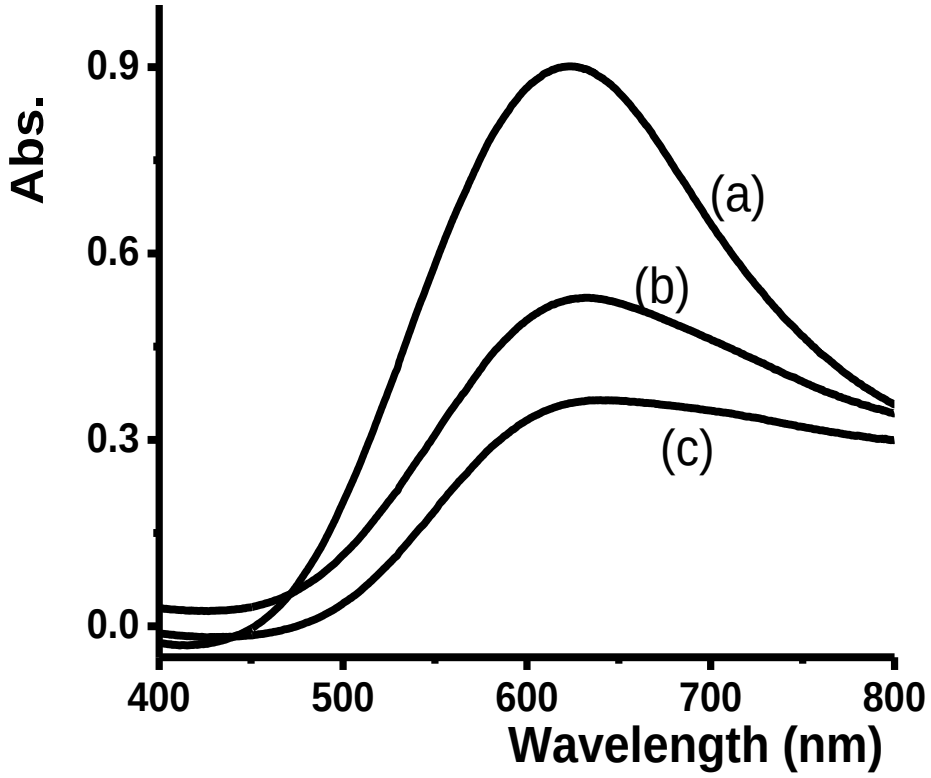


Figure 7 . Electronic Spectra of (a) **Complex 2** (b) **Complex 5** (c) **Complex 6**.

4. Solvatochromism of complexes

Complex **1** demonstrates solvatochromic in limited selected polar solvents like: water, EtOH, DMF and DMSO owing to its dicationic natural solubility. The electronic absorption spectra of such complexes were characterized by a broad structure band in the visible region attributed to d-d electron transition of the Cu(II) center. The visible spectral changes of complex **1** in some selected solvents are illustrated in **Figure 8**.

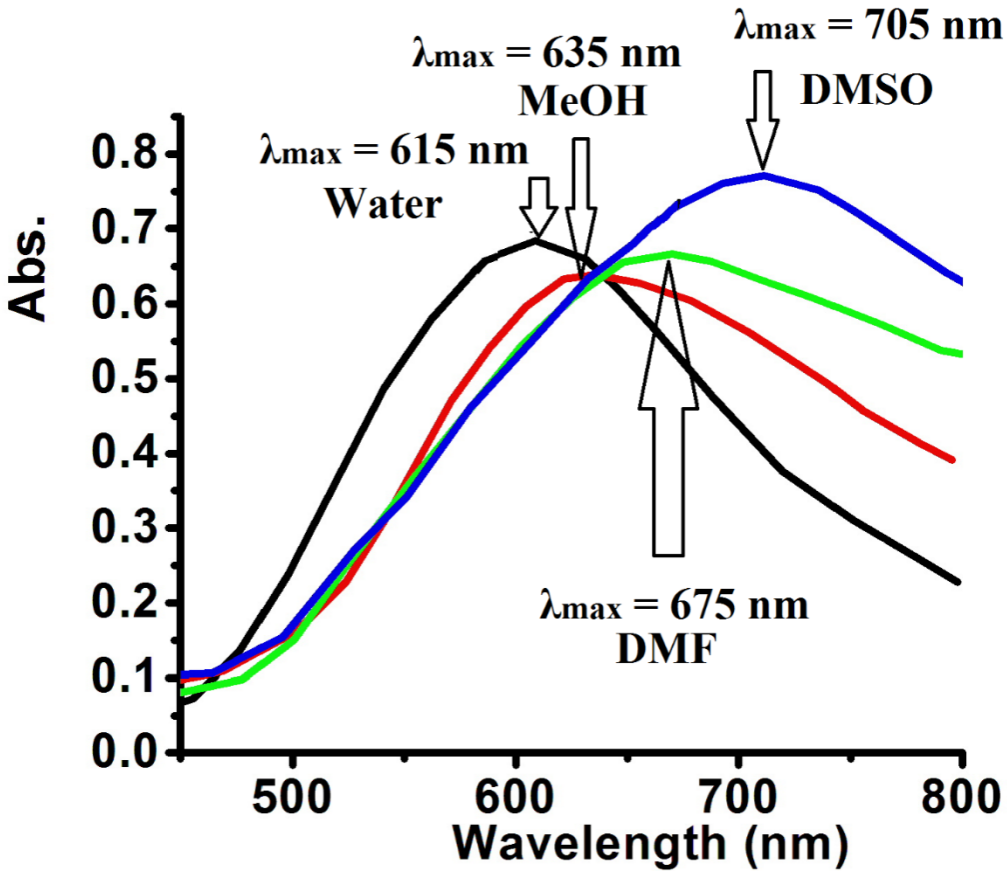


Figure 8. Absorption Spectra of Complex **1** in Some Selected Solvents.

The position of the λ_{max} was shifted to higher values, bathochromic color change shift was recorded, due to the direct coordination of polar solvent molecules onto the vacant sites of the square pyramide of Cu(II) center with different strength.

To explore the solvent effects on the absorption spectra of the complexes, $\lambda_{max,}$ values were plotted vs. Gutmann's donor DN and acceptor CN using solvatochromic Eq.2) as in **Figure 8**. The solvent parameters used include Gutmann's donor DN, acceptor numbers AN, electron pair donating ability β and hydrogen bonding ability α.

$$\upsilon_{\max} = \upsilon_{\max}^{\circ} + a\,\mathrm{DN} + b\,\mathrm{AN} + c\,\beta + d\,\alpha \qquad \text{…..2)}$$

Figure 9 reveals linear relation between λ_{max} values and DN but not CN, which indicates Lewis acidity of the complex against solvents donation. The results confirm the dominant contribution of DN parameter in the solvatochromism of the complex due to coordination of polar solvent molecules on the axial site of the Cu(II) center with different strength leading to a change in the geometry of the complex from square pyramide to octahedron [27-29].

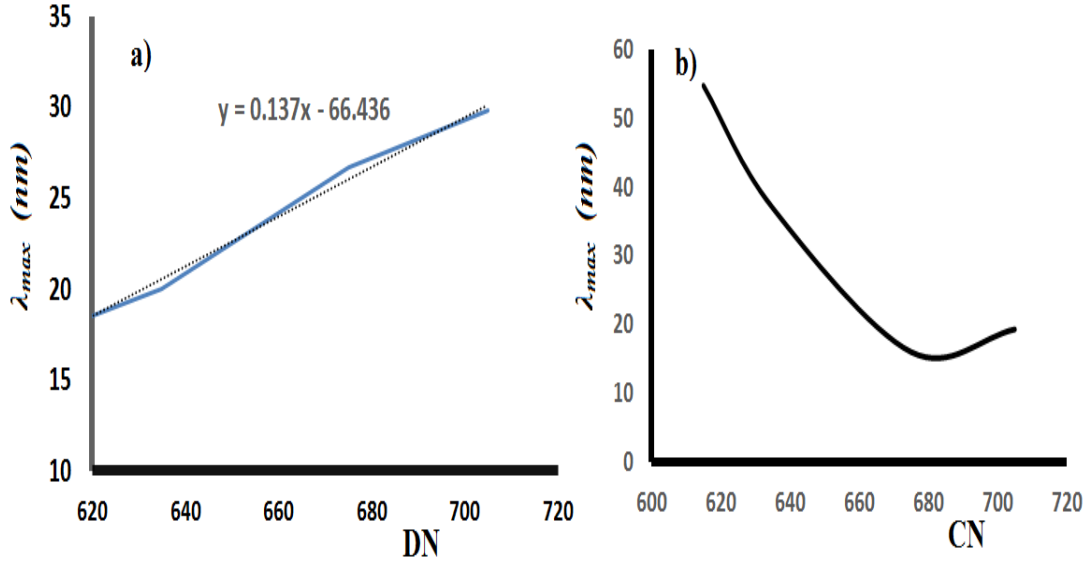


Figure 9. Dependence of the λ_{max} of complex **1** on the solvent Gutmann's donor DN (a) and acceptor CN (b).

5. IR Spectral Analysis

Several peaks were detected, due to the vibration of main functional groups. at ~ 3370 cm^{-1} and ~ 1480 cm^{-1}, assigned to water, $\nu_{(O\text{-}H)}$ and $\nu_{(bend)}$, respectively, which indicate the existence of molecular lattice water (as in XRD result). The two bands at 3350–3150 cm^{-1} and 1600–1500 cm^{-1} assigned to ν_s(N–H), ν_{as}(N–H) and δ(N–H) vibrations, are shifted to wave numbers lower than those encountered in the diamine/triamine ligands,

supporting their coordination to Cu(II) centre [42]. The strong bands at ~2900-2800 cm^{-1} are indexed to the stretching vibration of C-H of CH_2 in the dien and CH_3-group of Me_4en ligands [43]. The appearance of broad bands at ~ 600-500 cm^{-1} is mostly attributed to $\nu_{(Cu-N)}$ bond vibrations [44, 45]. Bands that are expected to appear at ~ 290-250 cm^{-1} region were assigned to the $\nu_{(Cu-X)}$ vibration [46]. IR spectrum of complexes **1** and **7** are given in **Figure 10**.

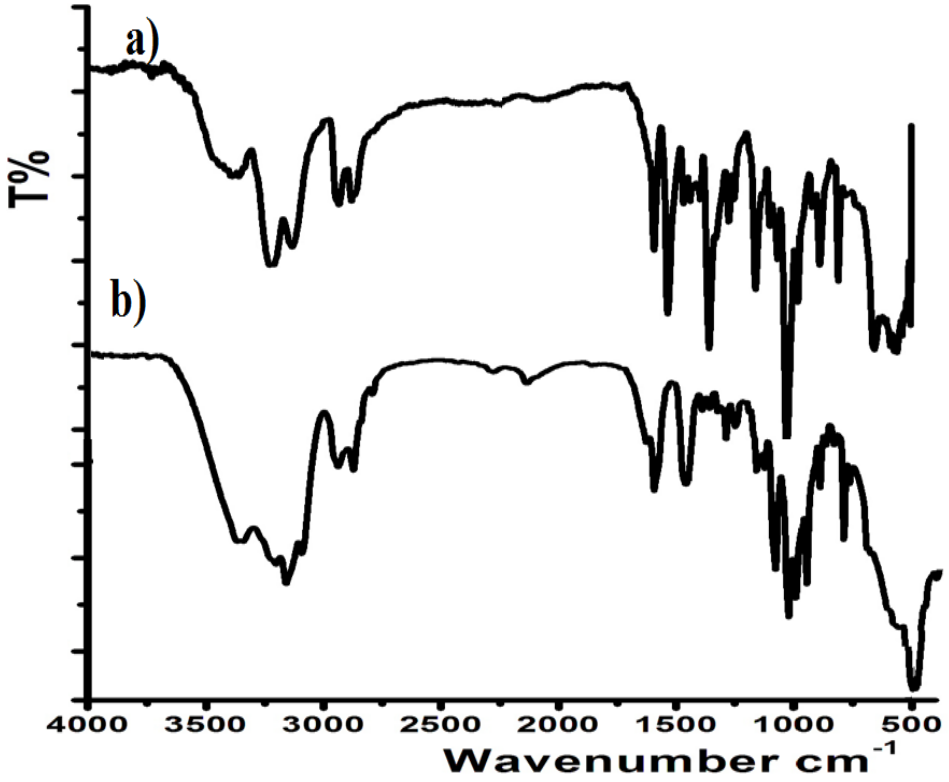


Figure 10. FT-IR Spectra of the Complex **1 (**a) and Complex **7(**b).

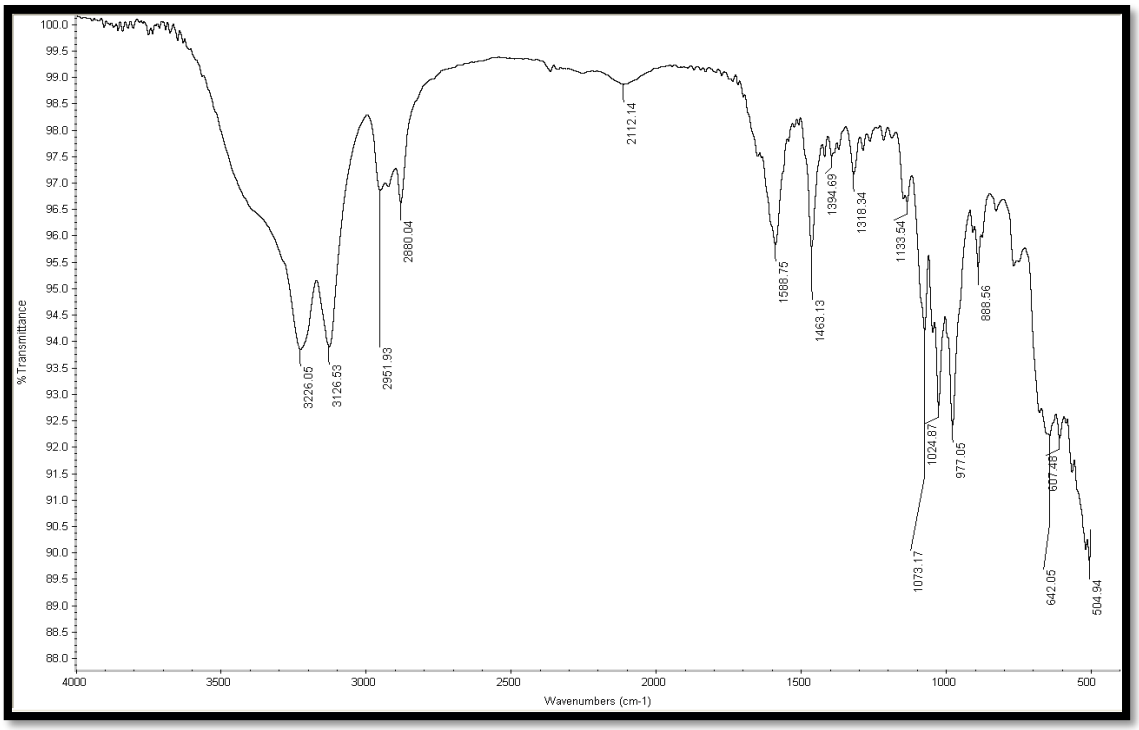


Figure 11. FT-IR Spectra of the **Complex 9**

6. Thermogravimetric analyses of complex 7

The TG/DTA curves were obtained at a heating rate of 5 ^{o}C min^{-1} in an open atmosphere over the temperature range of 0–1000 ^{o}C. The thermo gravimetric analyses of **complex 7** reveals the occurrence of four consecutive processes, namely, mono-dehydration, Me_4en followed by dien ligands pyrolysis and inorganic residue formation, as seen in **Figure 12**. The first decomposition step represents the loss of the uncoordinated water molecule in the range of 90-100 ^{o}C, losing ~3.5% at 92^{o}C, showing an endothermic sign of DTA. The second decomposition step starts at 160^{o}C and ends at 200^{o}C, losing ~25% of weight, due to Me_4en ligand de-structure, with DTA exothermic signs at 190^{o}C. The third decomposition step is registered between 210-350^{o}C losing ~23% of weight, due to the dien ligand loss, with DTA exothermic signs at 306^{o}C and $CuBr_2$ product

formation. The fourth decomposition step starts at 500°C and ends at 650°C, with DTA exothermic signs at 602°C which leads to the removal of bromide ions from $CuBr_2$ and reacts with oxygen to form copper oxide with 31.5% net weight loss. The final residue was analysed by IR spectra and identified as copper oxide (CuO, 17%) [31].

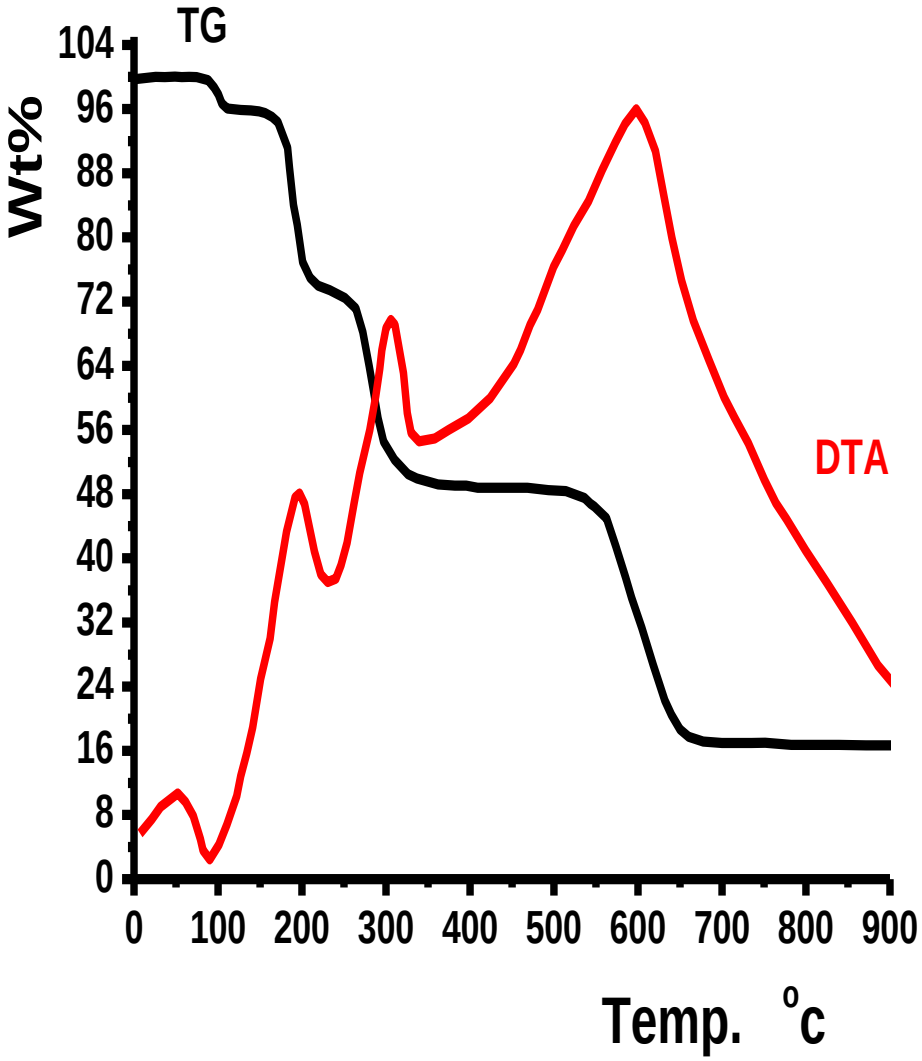


Figure 12 . TG/DTA Thermal Curve of the **Complex 7** .

7. Electrochemical behaviour of complex 7

Complex 7 was subjected to cyclic voltammetry in order to figure out its electrochemical behaviour. The electrochemical behaviour of the complex proceed through a quasi-reversible one electron process with unity anodic curves (oxidation curves) to cathodic curves (reduction curves) (Ipa/Ipc) ratio and - 0.78 V $E_{1/2}$value. During cyclic voltammetry experiment the Cu(I) species were generated with longer life time as shown in **Figure 13**.

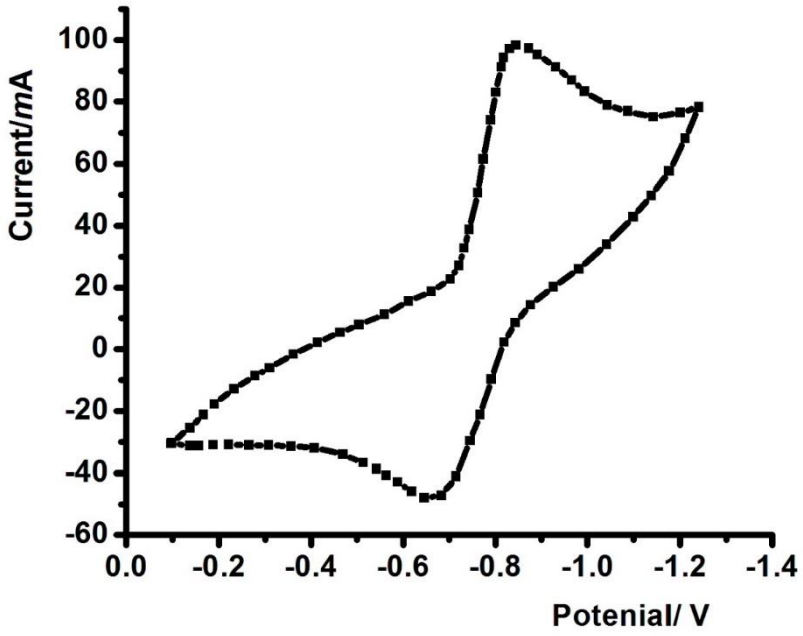


Figure 13. Cyclic Voltammogram of **Complex 7** in DMF Solvent in 0.1 M of $TBAPF_6$ Supporting Electrolyte.

The redox process can be formulated as follows:

$$[Cu(II)(dien)Me_4en)]^{2+} \longrightarrow [Cu(I)(dien)Me_4en)]^{+} \qquad E_{1/2} = -0.78\ V$$

The geometry of Cu (I) species changed from square pyramid into distorted tetrahedral during reduction process associated with the quasi-reversibility [31].

Chapter Three

Biological Application

Biological Activity

1. Bacterial isolates

Antibacterial activity of the Cu-complexes was evaluated against three reference bacterial isolates which are *Staphylococcus aureus* (ATCC25923), *Escherichia coli* (ATCC 25922) and *Pseudomonas aeruginosa* (ATCC 27853) all were obtained from the American Type Culture Collection (ATCC). In addition to that, four clinical isolates which are Methicillin resistant *Staphylococcus aureus* (MRSA), *Escherichia coli*, *Klebsiella pneumoniae* and *Proteus vulgaris* were also studied. Clinical isolates were obtained from Rafidia hospital and identified by Biology and Biotechnology Laboratory, An-Najah National University, Palestine.

2. Antibacterial activity of copper complexes

Disk diffusion method

The antibacterial activity of the investigated Cu-complexes was determined by disk diffusion method (NCCLS, 1999). The tested bacteria were grown over night on nutrient agar plates. Broth turbidity was adjusted to 0.5 McFarland (1.5×10^8 CFU/ml). Then each bacterium was inoculated by streaking the swab over the entire sterile Mueller-Hinton agar surface. This procedure was repeated by streaking two more times, rotating the plate approximately 60° each time to ensure an even distribution of the inoculum. As a final step, the rim of the agar was also swabbed. After 10 minutes

10 ml of 100 mg/ml of each complex under study was loaded to 6 mm disk and then the prepared disks were added to the surface of inoculated agar plates. The plates were allowed to stand at room temperature for 30 min for Cu- complexes to diffuse into the agar and then they were incubated at 37°C for 18 h. After incubation all plates were examined for bacterial growth inhibition by measuring the inhibition zone diameter (IZD) to the nearest mm. The test was performed in triplicates. Antibiotic Gentamicin (G) was used as positive control and sterilized distilled water was used as negative control.

Micro-broth dilution method

Minimum inhibitory concentration (MIC) for all Cu-complexes was determined by micro-broth dilution method (NCCLS, 2000). The prepared sample was serially diluted two fold in Mueller-Hinton broth medium. Duplicates of each dilution (1000, 500, 250, 125, 62.5, 31.25, 15.63, 7.8, 3.9 and 1.95 µg/ml) were inoculated with 1 µl of $5*10^7$ CFU/ml. The last two duplicate wells were not inoculated. After then, the inoculated microtiter plates were incubated at 37°C for 18 h. The lowest Cu-complex concentration (highest dilution) that inhibited the growth of tested micro organisms was considered as MIC. Minimum bacteriocidal concentration (MBC) was determined. In this technique, the contents of the wells resulting from MIC was streaked using a sterile cotton swaps on agar plate free of antibacterial agents and incubated at 37ºC for 18 hours. The lowest concentration of the Cu-complex which showed no bacterial growth was considered as MBC.

Results:

The in vitro biological screening effects of investigated Cu-complexes was tested by agar disk diffusion method. Copper complexes under study posses potential antibacterial activity against some bacterial isolates (Figure 14, 15). The obtained results showed that the studied Cu-complexes acted as antibacterial agents with different behaviors. It is clearly noticed that *S. aureus* (ATCC25923) and *E. coli* (ATCC 25922) were the most sensitive isolates as most of the Cu-complexes were more efficient than broad specific antibiotic Gentamicin. The most active complexes against *S. aureus* (ATCC25923) and *E.coli* (ATCC 25922) were **8**, **9** ,**6** complexes. The antibiotic resistant isolate MRSA showed moderate sensitivity to some of the examined complexes and complex **14** was the best among them with (14 mm) inhibition zone. Other clinical isolates *E. coli*, *K. pneumoniae* and *P. vulgaris* showed less or no sensitivity to the tested Cu-complexes. Complex **8** exhibited moderate bioactivity against *K. pneumoniae* with (12 mm) inhibition zone. On the other hand, and complex **5** showed antibacterial activity against

E. coli with (13 mm) inhibition zone. *P. aeruginosa* (ATCC 27853) was sensitive to complex **2** with (11 mm) inhibition zone.

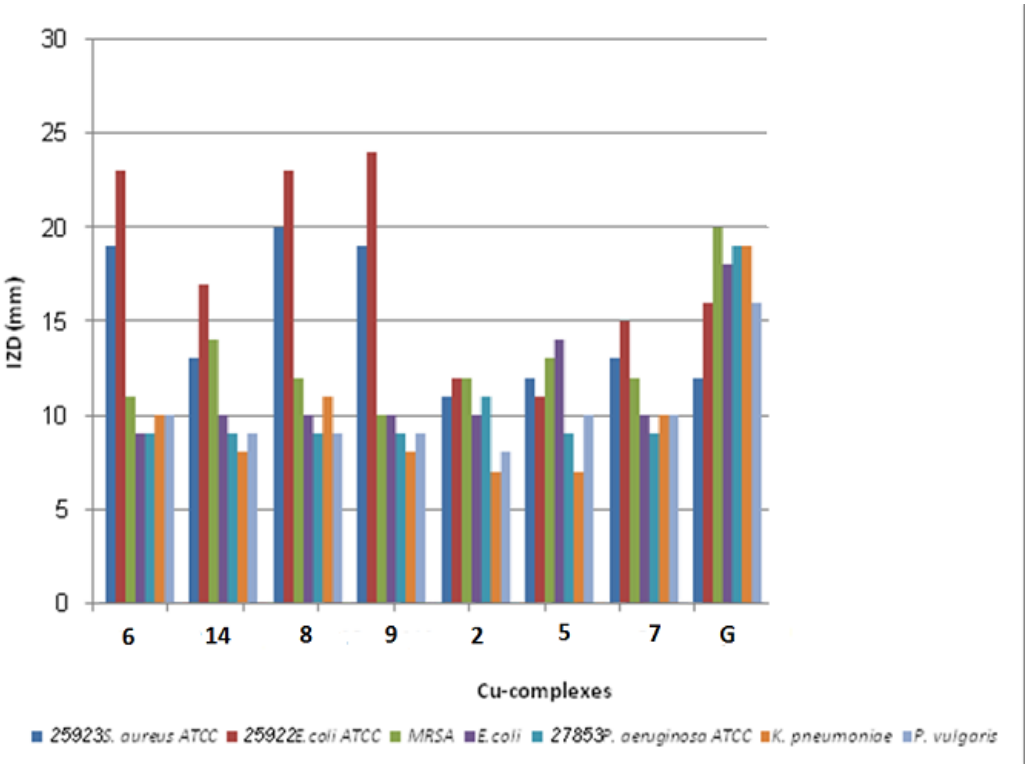


Figure 14: Antibacterial activity of Cu-Complexes (1mg/disk) Using Agar Disk Diffusion Method; (IZD) Inhibition Zone Diameter.

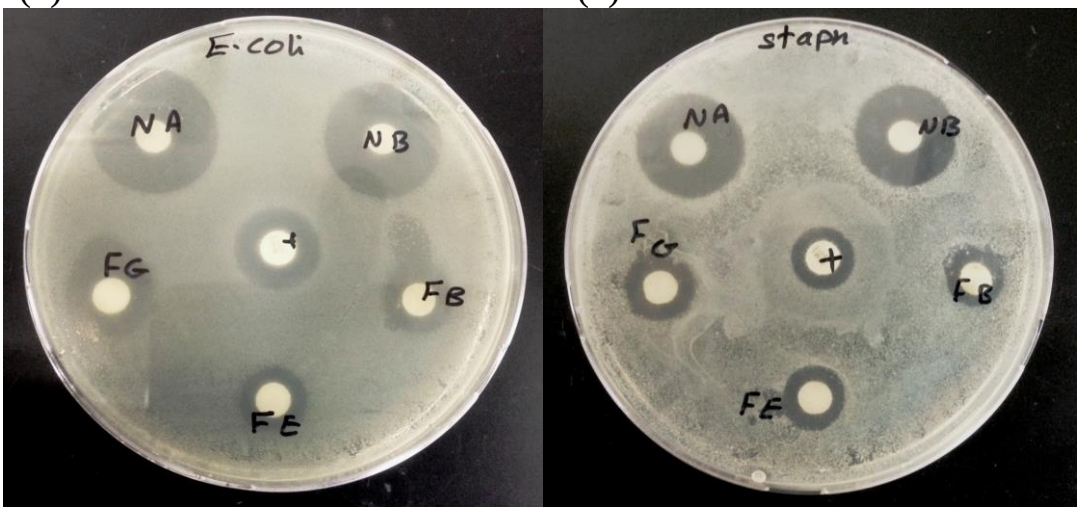
All Cu-complexes were further tested for their minimum inhibitory concentration (MIC) against the most sensitive isolates *S. aureus* (ATCC25923) and *E.coli* (ATCC 25922) (Table 2). The Gram positive bacterial isolate *S. aureus* (ATCC25923) was the most sensitive. It was inhibited by lower concentrations of all examined Cu-complexes when it was compared to the Gram negative bacterial isolate *E.coli* (ATCC 25922). **14**, **9** and **8** showed the same bioactivity against *E.coli* (ATCC 25922) with MIC values equal to 250 µg/ml.

Table 2: Antibacterial activity of Cu-complexes against *S. aureus* (ATCC25923) and *E.coli* (ATCC 25922) using micro-broth dilution method; (MIC) minimum inhibitory concentration (µg/ml), (MBC) minimum bactericidal concentration (µg/ml).

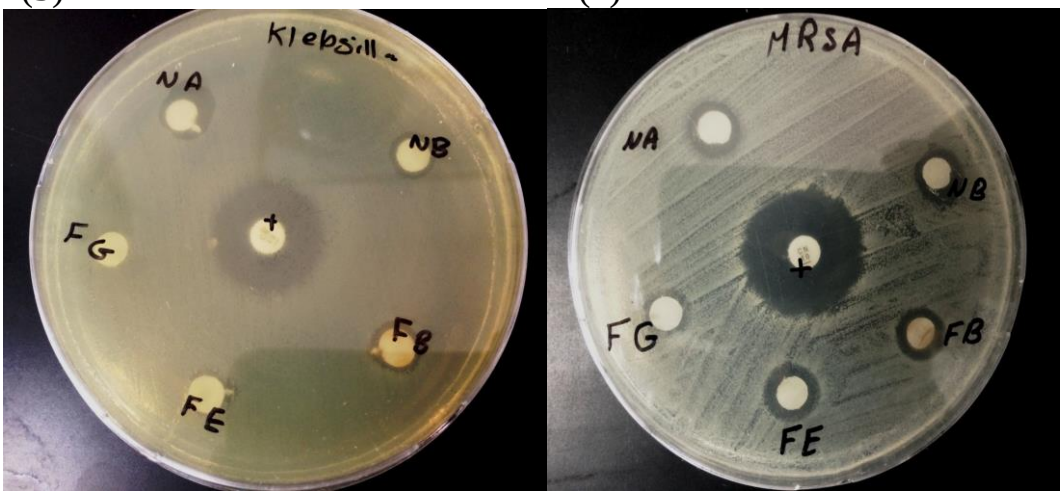
	14		8		9		2		5		7	
	MIC	MBC	MIC	MBC	MIC	MBC	MIC	MBC	MIC	MBC	MIC	MBC
S. aureus ATCC25923	500	500	125	1000	125	1000	500	2000	500	2000	500	1000
E.coli ATCC25922	250	250	250	1000	250	500	1000	2000	1000	2000	500	1000

The minimum bactericidal concentrations (MBC) for all Cu-complexes that were given inhibitory effect were determined. Table 2 showed that both 14 and 7 complexes had bactericidal activity at concentrations 500 and 1000 µg/ml respectively against *S. aureus* (ATCC25923). However the studied Cu-complexes were more effective as bactericidal agents against the Gram negative bacterial isolate *E.coli* (ATCC 25922). With complex **14** were the best as they killed *E.coli* (ATCC 25922) at 250 µg/ml.

(1) (2)



(3) (4)



(5)

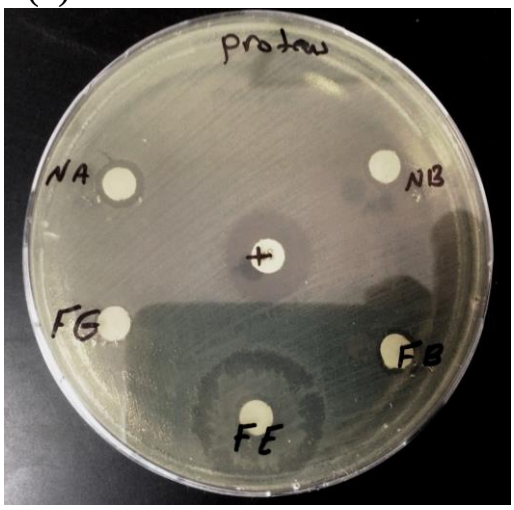


Figure 15: Antibacterial activity of Cu-Complexes (1mg/disk) Using Agar Disk Diffusion Method , NA = 8, NB= 9, FB=2, FE=5, FG=7, 1-E.coli 2-Staph. 3-klebsilla 4-MRSA 5-Proteus.

Discussion:

The emergence of multidrug resistant bacteria and their emphasis on the health care costs has provoked an interest in the design and development of novel and cost effective antimicrobial agents with increased bioactivity against resistant bacteria [59]. Metal based drugs represent a novel group of antimicrobial agents with potential applications for the control of various infectious diseases [50]. There are different factors that should be considered for the antimicrobial activity of metal complexes. These factors includes: the chelate effect (ligands that are bound to metal ions); the nature of the ligands; the total charge of the complex; the nature of the ion neutralizing the ionic complex and the nuclearity of the metal center in the complex [61-63].

In the present study, the in vitro antibacterial activity of several Cu-complexes was studied by disk diffusion method. The variable antibacterial activity of different Cu-complexes may be due to the different structures of synthesized Cu-complexes. It was reported that there was a relationship between a structure of Cu-complexes and their activity [49]. Copper complexes have plasticity as they are capable of assuming different shapes with different coordination numbers and thus adopt to substrate [52, 53]. Therefore, it was easily to adopt certain geometry and thus avoid possible steric hindrance during their physiological action [54].The observed variation in the activity of the copper complexes across the various types of the studied bacteria may be attributable to differences in cell wall and/or membrane construction [68].

Disk diffusion results provide evidence that the type of counter ion used in each complex may has an effect on the antibacterial activity of the studied Cu-complexes. **8** and **9** were the best antibacterial agents against S. aureus (ATCC25923) and E. coli (ATCC 25922) with inhibition zones (20 and 24 mm) respectively. Their activities were higher than the broad specific antibiotic Gentamicin. Among the studied Cu-complexes only **8**, **9** and **14** have chloride ions while the rest have bromide ions. The same observation was reported in an experiment done by [49]. In their experiment the synthesized Cu-complex with chloride counter ion was more powerful than Cu-complex with bromide counter ion. [51] Results showed that the selectivity of their complexes against some Gram positive and Gram negative bacteria were modulated by counter ions, which can coordinate to copper. The increased antibacterial activity of Cu-complexes with chloride counter ions may be due to solvolysis phenomenon. A lower solvation of the chloride salts of the complexes may enhance its antibacterial behavior [55]. It has been reported that presence of different copper ions and solvents (medium) affect the physicochemical properties of Cu-complexes and so their activities [58].Also, the bromide complexes display a lower stability than the corresponding chloride complexes [67].

It was clearly noticed that the examined Cu-complexes were more effective against Gram positive bacteria (*S. aureus*(ATCC25923) and MRSA).Studies showed that metal complexes with copper ions penetrate more easily through the bacterial cell wall, due to the proteic denaturation of the sulphydrile group, destroying the bacterial cell wall. In addition to

that copper complexes posses free N and NH groups can form hydrogen bonds with the peptidoglycan layer of the bacteria. This may be the reason for the better staphylococcal membrane damaging activity of the examined Cu-complexes [56]. The variation in the activity of Cu- complexes against some different organisms depends on either the impermeability of the cells of the microbes or difference in ribosome of microbial cells [57].

Chapter Four

Experimental part

Types of Bacteria that were studied:

1- *Klebsiella*

The Klebsiella genus consists of diverse organisms that are capable of colonizing and causing disease in humans and animals or existing as endophytes that colonize plants.

2- *Escherichia coli*

Escherichia coli (E.coli) is arod-shaped, Gram-negative bacterium found in high numbers in the gut of warm-blooded animals. For over 100 years, it has been used to detect faecal contamination in water and as an indicator of waterborne disease risk.

3- *Proteus*

Gram-negative bacteria of the genus Proteus belong to the Enterobacteriaceae family. They are present in the intestines of human and animals and are opportunistic pathogens. In addition, Proteus bacteria may be associated with nosocomial infections and can cause hematogenous and ascending infections.

4- *Staphylococcus aureus*

is a Gram-positive human pathogen, S.aureus has forward to a major problem in hospital settings since effective treatment options for contagions caused by this pathogen are limited.

2. Methods

a. Chemical reagents

Diethylenetriamine, diamines and $CuX_2.2H_2O$ were purchased from Sigma–Aldrich and in analytical grade purities.

b. Physical Measurements

(C, H, and N) microanalyses were carried out using an Elementar Varrio EL analyzer. "The FT-IR spectra (4000–400 cm^{-1}) were obtained from KBr discs with a Perkin–Elmer 621 spectrophotometer. Thermal analyses, thermogravimetry (TG) and differential thermal analysis (DTA) were carried out with TA Instruments SDT-Q600 in air. Electronic spectra were recorded in water at room temperature (RT) on Pharmacia LKB-Biochrom 4060 spectrophotometer. The electrochemical properties of the complex **2** were investigated by cyclic voltammetry in DMF solutions containing 0.1 M of $TBAPF_6$ as a supporting electrolyte. Cyclic voltammograms were recorded at scan rate 0.1V vs Ag/AgCl." The Hirshfeld surface analysis of **complex 7** was carried out using the program CRYSTAL EXPLORER 3.1 [32].

c. X-Ray Single-Crystal Data collection

A solution of complexes **(1-7)** in water and subsequently water slowly evaporated. Elongated blue single crystal was selected and collected on a Bruker SMART Apex II diffractometer equipped with a CCD area detector at 150(2) K with monochromated Mo-Kα radiation (λ = 0.71073 Å). The crystal was positioned at 40 mm from the CCD and the spots were measured using 20 s counting time. The SAINT-NT software package was used for data reduction [33]. The SADABS program was applied for multi-scan absorption correction to all intensity data [34]. The SHELX-2013 was used to solve the structure of the complex [35]. All non-hydrogen atoms were refined with anisotropic thermal displacements. The C-H hydrogen atoms were included in the structure refinement in geometrically idealized

positions and $U_{iso}=1/2U_{eq}$ (parent carbon atom). The N-H and O-H hydrogens were obtained by—different electron density synthesis and refined by O…H distance restraints of 0.83 Å. Molecular and crystal packing diagrams were drawn with Platon software package [36]. Details of crystal data collection and refinement are given in **Table3**.

Table 3. Crystal data and refinement parameters for complex 7.*H_2O*.

Empirical Formula	$C_{10}H_{31}Br_2CuN_5O$
M_w	460.76
CrystalSystem	Monoclinic
Spacegroup	*$P2_1/n$*
a/ [Å]	8.4202(15)
b/ [Å]	24.246(4)
c / [Å]	9.0117(16)
α / [º]	90
β / [º]	98.549(9)
γ / [º]	90
V [Å^3]	1819.3(6)
Z	4
D_c [Mg m^{-3}]	1.682
μ / [mm^{-1}]	5.594
F(000)	932
Crystal size [mm]	0.20 x 0.10 x 0.06
θ range data collection	1.680 – 29.299
Index ranges	$-10\leq h\leq 11, -32\leq k\leq 33, -12\leq l\leq 12$
Reflections collected	32881
Unique reflections, [R_{int}]	4967 [0.0601]
Final *R*indices	
R_1, wR_2 [$I>2\sigma I$]	0.0285, 0.0581 [3905]
R_1, wR_2 (all data)	0.0444, 0.0628
Goodness of fit on F^2	0.997

Table 4. Total bond length in complex 7

Number	Atom1	Atom2	Length
1	H1A	N1	0.91(3)
2	H1B	N1	0.80(2)
3	H2A	C2	0.99
4	H2B	C2	0.99

5	H3A	C3	0.991
6	H3B	C3	0.99
7	H4	N4	0.80(2)
8	H5A	C5	0.989
9	H5B	C5	0.99
10	H6A	C6	0.99
11	H6B	C6	0.99
12	H7A	N7	0.82(3)
13	H7B	N7	0.86(2)
14	H9A	C9	0.98
15	H9B	C9	0.98
16	H9C	C9	0.98
17	H10A	C10	0.98
18	H10B	C10	0.98
19	H10C	C10	0.979
20	H11A	C11	0.991
21	H11B	C11	0.99
22	H12A	C12	0.991
23	H12B	C12	0.99
24	H14A	C14	0.981
25	H14B	C14	0.979
26	H14C	C14	0.98
27	H15A	C15	0.979
28	H15B	C15	0.979
29	H15C	C15	0.981
30	C2	C3	1.510(3)
31	C2	N1	1.476(4)
32	C3	N4	1.473(3)
33	C5	C6	1.509(4)
34	C5	N4	1.470(3)
35	C6	N7	1.471(3)
36	C9	N8	1.476(3)
37	C10	N8	1.472(3)
38	C11	C12	1.510(3)
39	C11	N8	1.477(3)
40	C12	N13	1.483(3)
41	C14	N13	1.487(3)
42	C15	N13	1.485(3)
43	N1	Cu	2.045(2)
44	N4	Cu	2.025(2)
45	N7	Cu	2.035(2)
46	N8	Cu	2.287(2)
47	N13	Cu	2.093(2)
48	H10D	O100	0.83(2)
49	H10E	O100	0.83(3)

Table 5. Total angles in complex 7

Number	Atom1	Atom2	Atom3	Angle
1	H2A	C2	H2B	108.6
2	H2A	C2	C3	110.3
3	H2A	C2	N1	110.4
4	H2B	C2	C3	110.3
5	H2B	C2	N1	110.3
6	C3	C2	N1	106.9(2)
7	H3A	C3	H3B	108.6
8	H3A	C3	C2	110.4
9	H3A	C3	N4	110.4
10	H3B	C3	C2	110.4
11	H3B	C3	N4	110.5
12	C2	C3	N4	106.5(2)
13	H5A	C5	H5B	108.6
14	H5A	C5	C6	110.3
15	H5A	C5	N4	110.2
16	H5B	C5	C6	110.3
17	H5B	C5	N4	110.2
18	C6	C5	N4	107.1(2)
19	H6A	C6	H6B	108.6
20	H6A	C6	C5	110.2
21	H6A	C6	N7	110.2
22	H6B	C6	C5	110.2
23	H6B	C6	N7	110.2
24	C5	C6	N7	107.5(2)
25	H9A	C9	H9B	109.5
26	H9A	C9	H9C	109.5
27	H9A	C9	N8	109.5
28	H9B	C9	H9C	109.4
29	H9B	C9	N8	109.5
30	H9C	C9	N8	109.5
31	H10A	C10	H10B	109.4
32	H10A	C10	H10C	109.5
33	H10A	C10	N8	109.4
34	H10B	C10	H10C	109.5
35	H10B	C10	N8	109.5
36	H10C	C10	N8	109.5
37	H11A	C11	H11B	108.1
38	H11A	C11	C12	109.5

39	H11A	C11	N8	109.4
40	H11B	C11	C12	109.5
41	H11B	C11	N8	109.5
42	C12	C11	N8	110.7(2)
43	H12A	C12	H12B	108.1
44	H12A	C12	C11	109.4
45	H12A	C12	N13	109.5
46	H12B	C12	C11	109.4
47	H12B	C12	N13	109.4
48	C11	C12	N13	111.0(2)
49	H14A	C14	H14B	109.5
50	H14A	C14	H14C	109.5
51	H14A	C14	N13	109.4
52	H14B	C14	H14C	109.5
53	H14B	C14	N13	109.4
54	H14C	C14	N13	109.5
55	H15A	C15	H15B	109.6
56	H15A	C15	H15C	109.5
57	H15A	C15	N13	109.5
58	H15B	C15	H15C	109.4
59	H15B	C15	N13	109.5
60	H15C	C15	N13	109.4
61	H1A	N1	H1B	109(2)
62	H1A	N1	C2	110(2)
63	H1A	N1	Cu	116(2)
64	H1B	N1	C2	111(2)
65	H1B	N1	Cu	103(2)
66	C2	N1	Cu	108.7(2)
67	H4	N4	C3	105(2)
68	H4	N4	C5	111(2)
69	H4	N4	Cu	107(2)
70	C3	N4	C5	114.3(2)
71	C3	N4	Cu	109.8(1)
72	C5	N4	Cu	109.6(2)
73	H7A	N7	H7B	106(3)
74	H7A	N7	C6	111(2)
75	H7A	N7	Cu	116(2)
76	H7B	N7	C6	111(2)
77	H7B	N7	Cu	103(2)
78	C6	N7	Cu	110.1(1)
79	C9	N8	C10	108.0(2)

80	C9	N8	C11	111.0(2)
81	C9	N8	Cu	112.3(1)
82	C10	N8	C11	108.6(2)
83	C10	N8	Cu	115.7(1)
84	C11	N8	Cu	101.0(1)
85	C12	N13	C14	110.2(2)
86	C12	N13	C15	108.2(2)
87	C12	N13	Cu	105.6(1)
88	C14	N13	C15	106.4(2)
89	C14	N13	Cu	113.0(1)
90	C15	N13	Cu	113.4(1)
91	N1	Cu	N4	82.91(8)
92	N1	Cu	N7	154.18(8)
93	N1	Cu	N8	105.55(7)
94	N1	Cu	N13	94.60(8)
95	N4	Cu	N7	82.81(8)
96	N4	Cu	N8	102.35(7)
97	N4	Cu	N13	173.61(8)
98	N7	Cu	N8	98.46(7)
99	N7	Cu	N13	97.26(7)
100	N8	Cu	N13	83.98(6)
101	H10D	O100	H10E	106(3)

Table 6. Total torsion in complex 7

Number	Atom1	Atom2	Atom3	Atom4	Torsion
1	H2A	C2	C3	H3A	-65.2
2	H2A	C2	C3	H3B	54.9
3	H2A	C2	C3	N4	174.9
4	H2B	C2	C3	H3A	54.7
5	H2B	C2	C3	H3B	174.9
6	H2B	C2	C3	N4	-65.2
7	N1	C2	C3	H3A	174.7
8	N1	C2	C3	H3B	-65.1
9	N1	C2	C3	N4	54.8(2)
10	H2A	C2	N1	H1A	71
11	H2A	C2	N1	H1B	-50
12	H2A	C2	N1	Cu	-162
13	H2B	C2	N1	H1A	-49
14	H2B	C2	N1	H1B	-170
15	H2B	C2	N1	Cu	78
16	C3	C2	N1	H1A	-169(2)

17	C3	C2	N1	H1B	70(2)
18	C3	C2	N1	Cu	-42.0(2)
19	H3A	C3	N4	H4	-47
20	H3A	C3	N4	C5	75
21	H3A	C3	N4	Cu	-161.4
22	H3B	C3	N4	H4	-167
23	H3B	C3	N4	C5	-45.1
24	H3B	C3	N4	Cu	78.5
25	C2	C3	N4	H4	73(2)
26	C2	C3	N4	C5	-165.1(2)
27	C2	C3	N4	Cu	-41.5(2)
28	H5A	C5	C6	H6A	-172.1
29	H5A	C5	C6	H6B	-52.3
30	H5A	C5	C6	N7	67.9
31	H5B	C5	C6	H6A	-52.1
32	H5B	C5	C6	H6B	67.7
33	H5B	C5	C6	N7	-172.1
34	N4	C5	C6	H6A	67.9
35	N4	C5	C6	H6B	-172.3
36	N4	C5	C6	N7	-52.2(2)
37	H5A	C5	N4	H4	164
38	H5A	C5	N4	C3	45.8
39	H5A	C5	N4	Cu	-77.9
40	H5B	C5	N4	H4	44
41	H5B	C5	N4	C3	-74.2
42	H5B	C5	N4	Cu	162.2
43	C6	C5	N4	H4	-76(2)
44	C6	C5	N4	C3	165.8(2)
45	C6	C5	N4	Cu	42.2(2)
46	H6A	C6	N7	H7A	47
47	H6A	C6	N7	H7B	165
48	H6A	C6	N7	Cu	-82.5
49	H6B	C6	N7	H7A	-73
50	H6B	C6	N7	H7B	45
51	H6B	C6	N7	Cu	157.8
52	C5	C6	N7	H7A	167(2)
53	C5	C6	N7	H7B	-75(2)
54	C5	C6	N7	Cu	37.6(2)
55	H9A	C9	N8	C10	-60.4
56	H9A	C9	N8	C11	-179.4
57	H9A	C9	N8	Cu	68.3

58	H9B	C9	N8	C10	179.5
59	H9B	C9	N8	C11	60.5
60	H9B	C9	N8	Cu	-51.8
61	H9C	C9	N8	C10	59.6
62	H9C	C9	N8	C11	-59.4
63	H9C	C9	N8	Cu	-171.7
64	H10A	C10	N8	C9	-179.5
65	H10A	C10	N8	C11	-58.9
66	H10A	C10	N8	Cu	53.8
67	H10B	C10	N8	C9	60.6
68	H10B	C10	N8	C11	-178.9
69	H10B	C10	N8	Cu	-66.2
70	H10C	C10	N8	C9	-59.5
71	H10C	C10	N8	C11	61
72	H10C	C10	N8	Cu	173.7
73	H11A	C11	C12	H12A	179.7
74	H11A	C11	C12	H12B	-62.1
75	H11A	C11	C12	N13	58.8
76	H11B	C11	C12	H12A	-61.9
77	H11B	C11	C12	H12B	56.3
78	H11B	C11	C12	N13	177.2
79	N8	C11	C12	H12A	58.9
80	N8	C11	C12	H12B	177.1
81	N8	C11	C12	N13	-62.0(2)
82	H11A	C11	N8	C9	160.8
83	H11A	C11	N8	C10	42.2
84	H11A	C11	N8	Cu	-79.9
85	H11B	C11	N8	C9	42.5
86	H11B	C11	N8	C10	-76.1
87	H11B	C11	N8	Cu	161.8
88	C12	C11	N8	C9	-78.3(2)
89	C12	C11	N8	C10	163.0(2)
90	C12	C11	N8	Cu	40.9(2)
91	H12A	C12	N13	C14	161.6
92	H12A	C12	N13	C15	45.6
93	H12A	C12	N13	Cu	-76.1
94	H12B	C12	N13	C14	43.3
95	H12B	C12	N13	C15	-72.6
96	H12B	C12	N13	Cu	165.7
97	C11	C12	N13	C14	-77.5(2)
98	C11	C12	N13	C15	166.5(2)

99	C11	C12	N13	Cu	44.8(2)
100	H14A	C14	N13	C12	-61.9
101	H14A	C14	N13	C15	55.3
102	H14A	C14	N13	Cu	-179.7
103	H14B	C14	N13	C12	178.2
104	H14B	C14	N13	C15	-64.7
105	H14B	C14	N13	Cu	60.3
106	H14C	C14	N13	C12	58.1
107	H14C	C14	N13	C15	175.3
108	H14C	C14	N13	Cu	-59.7
109	H15A	C15	N13	C12	64.4
110	H15A	C15	N13	C14	-54
111	H15A	C15	N13	Cu	-178.8
112	H15B	C15	N13	C12	-55.7
113	H15B	C15	N13	C14	-174.1
114	H15B	C15	N13	Cu	61.1
115	H15C	C15	N13	C12	-175.6
116	H15C	C15	N13	C14	65.9
117	H15C	C15	N13	Cu	-58.8
118	H1A	N1	Cu	N4	139(2)
119	H1A	N1	Cu	N7	-164(2)
120	H1A	N1	Cu	N8	38(2)
121	H1A	N1	Cu	N13	-47(2)
122	H1B	N1	Cu	N4	-102(2)
123	H1B	N1	Cu	N7	-45(2)
124	H1B	N1	Cu	N8	157(2)
125	H1B	N1	Cu	N13	72(2)
126	C2	N1	Cu	N4	15.5(2)
127	C2	N1	Cu	N7	72.3(3)
128	C2	N1	Cu	N8	-85.4(2)
129	C2	N1	Cu	N13	-170.5(2)
130	H4	N4	Cu	N1	-99(2)
131	H4	N4	Cu	N7	103(2)
132	H4	N4	Cu	N8	6(2)
133	H4	N4	Cu	N13	-166(2)
134	C3	N4	Cu	N1	14.9(1)
135	C3	N4	Cu	N7	-143.5(2)
136	C3	N4	Cu	N8	119.3(1)
137	C3	N4	Cu	N13	-52.5(8)
138	C5	N4	Cu	N1	141.1(2)
139	C5	N4	Cu	N7	-17.3(2)

140	C5	N4	Cu	N8	-114.4(2)
141	C5	N4	Cu	N13	73.7(7)
142	H7A	N7	Cu	N1	165(2)
143	H7A	N7	Cu	N4	-138(2)
144	H7A	N7	Cu	N8	-37(2)
145	H7A	N7	Cu	N13	48(2)
146	H7B	N7	Cu	N1	49(2)
147	H7B	N7	Cu	N4	106(2)
148	H7B	N7	Cu	N8	-152(2)
149	H7B	N7	Cu	N13	-67(2)
150	C6	N7	Cu	N1	-68.6(3)
151	C6	N7	Cu	N4	-11.8(2)
152	C6	N7	Cu	N8	89.7(2)
153	C6	N7	Cu	N13	174.7(1)
154	C9	N8	Cu	N1	12.0(2)
155	C9	N8	Cu	N4	-74.0(2)
156	C9	N8	Cu	N7	-158.4(1)
157	C9	N8	Cu	N13	105.1(1)
158	C10	N8	Cu	N1	136.6(1)
159	C10	N8	Cu	N4	50.6(2)
160	C10	N8	Cu	N7	-33.8(2)
161	C10	N8	Cu	N13	-130.3(2)
162	C11	N8	Cu	N1	-106.4(1)
163	C11	N8	Cu	N4	167.6(1)
164	C11	N8	Cu	N7	83.2(1)
165	C11	N8	Cu	N13	-13.3(1)
166	C12	N13	Cu	N1	88.9(1)
167	C12	N13	Cu	N4	155.8(7)
168	C12	N13	Cu	N7	-114.1(1)
169	C12	N13	Cu	N8	-16.3(1)
170	C14	N13	Cu	N1	-150.5(1)
171	C14	N13	Cu	N4	-83.7(7)
172	C14	N13	Cu	N7	6.5(1)
173	C14	N13	Cu	N8	104.3(1)
174	C15	N13	Cu	N1	-29.4(2)
175	C15	N13	Cu	N4	37.4(8)
176	C15	N13	Cu	N7	127.6(1)
177	C15	N13	Cu	N8	-134.6(1)

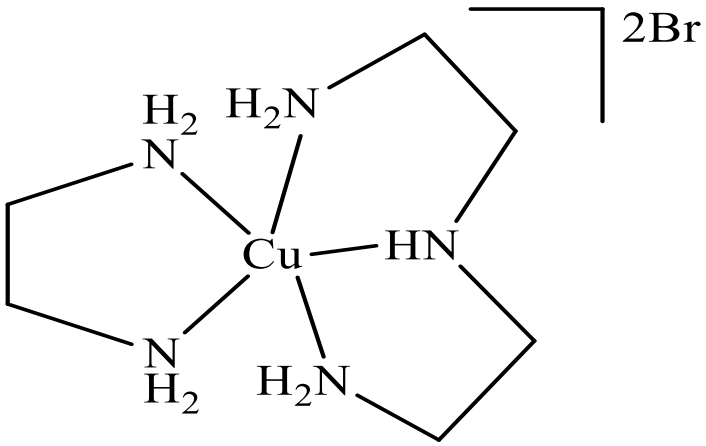
2. Synthetic method for the target complexes (1-14)

1 mmol of $CuX_2.H_2O$ was dissolved in 20 ml methanol and 1.1 mmol of diamine or triamine was dissolved in 2 ml of methanol.

The two solutions were mixed together and the mixture was subjected to Ultrasound waves for 30 minutes till a deep blue colour is obtained. The solvent was removed by vacuum. The residue was washed with 20 ml methylene chloride and then with isopropanol. The solid product was crystallized from water.

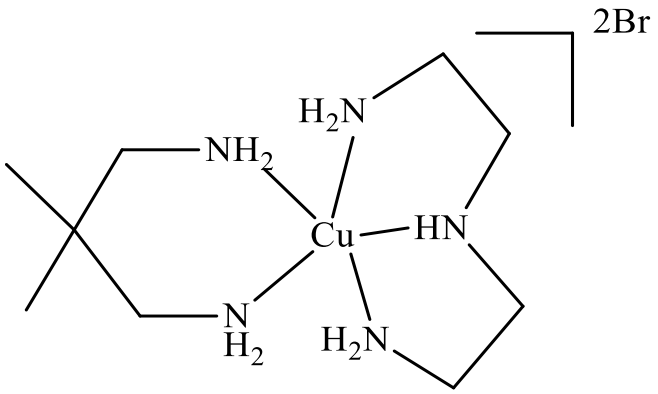
No. of Complexes:

Complex 1:



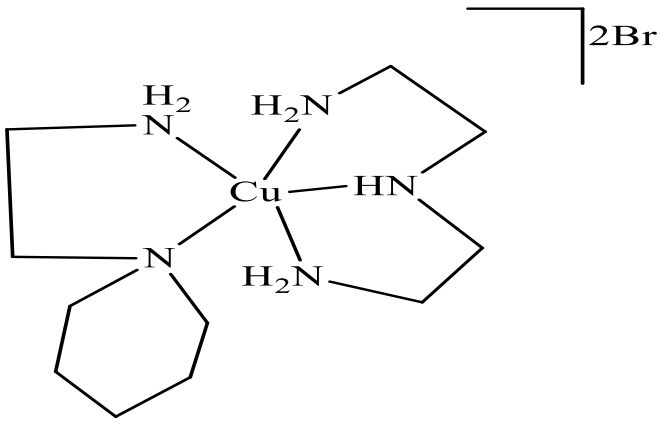
MS *m/z* 226.2 [M+] for $C_6H_{21}Br_2CuN_5$ Calculated: C, 18.64; H, 5.47; N, 18.11. Found C, 18.41; H, 5.35; N, 18.09%, IR (KBr, νcm^{-1}): 3350 (ν_{H2O}), 3370 and 3268 and 3125 (ν_{H-N}), 2940 (ν_{C-H}), 1585 (ν_{N-H}), 1150 (ν_{N-C}), 520 (ν_{Cu-N}).UV–Vis.(in H_2O): λ_{max} (ε_{max} /M^{-1} cm^{-1}): 250 nm (1.50 x 10^3 $M^{-1}L^{-1}$) and 605 nm (2.80 x 10^2 $M^{-1}L^{-1}$); M.p. = 125 °C; Yield 92%

Complex 2:



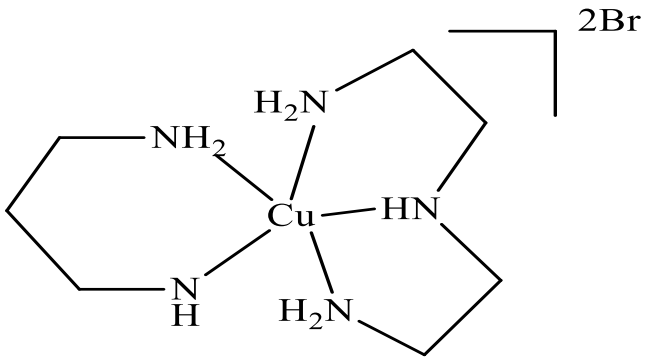
MS m/z: 324.22 for $C_{13}H_{35}Br_2CuN_5$. Calculated: C, 32.21; H, 7.28; N, 14.45. Found C, 20.41; H, 6.35; N, 16.09%, IR (KBr, νcm^{-1}): 3360 (ν_{H2O}), 3355 and 3260 and 3130 (ν_{H-N}), 2935 (ν_{C-H}), 1575 (ν_{N-H}), 1160 (ν_{N-C}), 517 (ν_{Cu-N}).UV–Vis.(in H_2O): λ_{max} (ε_{max} /M^{-1} cm^{-1}): 245 nm (1.40 x 10^3 $M^{-1}L^{-1}$) and 620 nm (2.95 x 10^2 $M^{-1}L^{-1}$); M.p. = 135 °C; Yield 70%.

Complex 3:



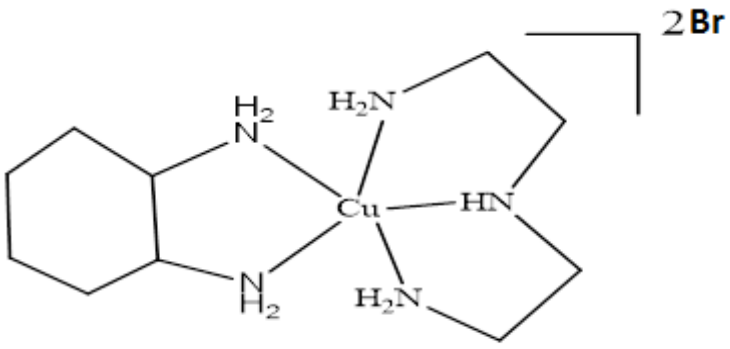
MS m/z: 294.17 for $C_{11}H_{29}Br_2CuN_5$. Calculated: C, 29.05; H, 6.43; N, 15.40. Found C, 19.31; H, 5.95; N, 16.59%, IR (KBr, νcm^{-1}): 3355 (ν_{H2O}), 3340 and 3275 and 3140 (ν_{H-N}), 2945 (ν_{C-H}), 1580 (ν_{N-H}), 1154 (ν_{N-C}), 519 (ν_{Cu-N}).UV–Vis.(in H_2O): λ_{max} (ε_{max} /M^{-1} cm^{-1}): 253 nm (1.33 x 10^3 $M^{-1}L^{-1}$) and 615 nm (2.75 x 10^2 $M^{-1}L^{-1}$); M.p. = 140 °C; Yield 71%.

Complex 4:



MS m/z: 240.12 for $C_7H_{23}Br_2CuN_5$. Calculated: C, 20.98; H, 5.79; Br, 39.89; Cu, 15.86; N, 17.48. Found C, 25.08; H, 6.50; N, 17.68%, IR (KBr, νcm^{-1}): 3366 (ν_{H2O}), 3360, 3250 and 3135, (ν_{H-N}), 2925 (ν_{C-H}), 1570 (ν_{N-H}), 1165 (ν_{N-C}), 525 (ν_{Cu-N}). UV–Vis. (in H_2O): λ_{max} (ε_{max} /M^{-1} cm^{-1}): 249 nm (1.25 x 10^3 $M^{-1}L^{-1}$) and 625 nm (3.10 x 10^2 $M^{-1}L^{-1}$); M.p. = 143 °C; Yield 74%.

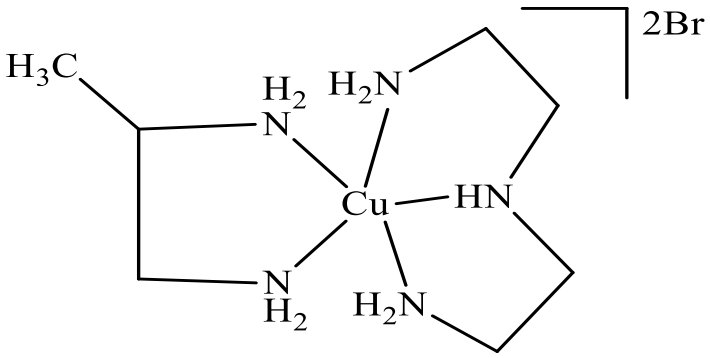
Complex 5:



MS m/z: 252.13 for $C_8H_{23}Br_2CuN_5$. Calculated: C, 23.28; H, 5.62; Br, 38.73; Cu, 15.40; N, 16.97. Found C, 22.55; H, 5.53; N, 18.78%, IR (KBr, νcm^{-1}): 3364 (ν_{H2O}), 3366, 3255 and 3145, (ν_{H-N}), 2930 (ν_{C-H}), 1565 (ν_{N-H}),

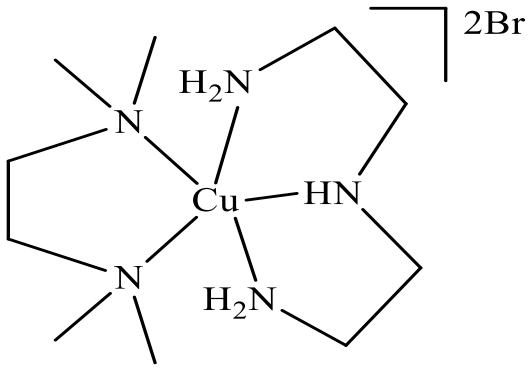
1152 (ν_{N-C}), 518 (ν_{Cu-N}). UV–Vis. (in H_2O): λ_{max} (ε_{max} /M^{-1} cm^{-1}): 257 nm (1.29 x 10^3 $M^{-1}L^{-1}$) and 611 nm (3.00 x 10^2 $M^{-1}L^{-1}$); M.p. = 153 °C; Yield 72%.

Complex 6:



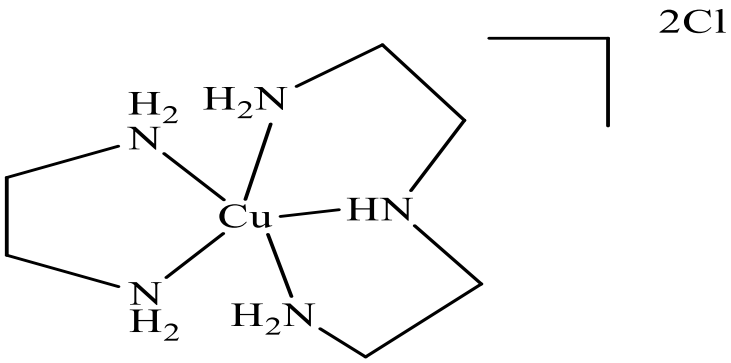
MS m/z: 240.12 for $C_7H_{23}Br_2CuN_5$ .Calculated: C, 20.98; H, 5.79; N, 17.48. Found C, 23.08; H, 5.54; N, 18.68%, IR (KBr, νcm^{-1}): 3354 (ν_{H2O}), 3366, 3255 and 3145, (ν_{H-N}), 2930 (ν_{C-H}), 1565 (ν_{N-H}), 1152 (ν_{N-C}), 518 (ν_{Cu-N}). UV–Vis. (in H_2O): λ_{max} (ε_{max} /M^{-1} cm^{-1}): 257 nm (1.29 x 10^3 $M^{-1}L^{-1}$) and 611 nm (3.00 x 10^2 $M^{-1}L^{-1}$); M.p. = 156 °C; Yield 78%.

Complex 7:



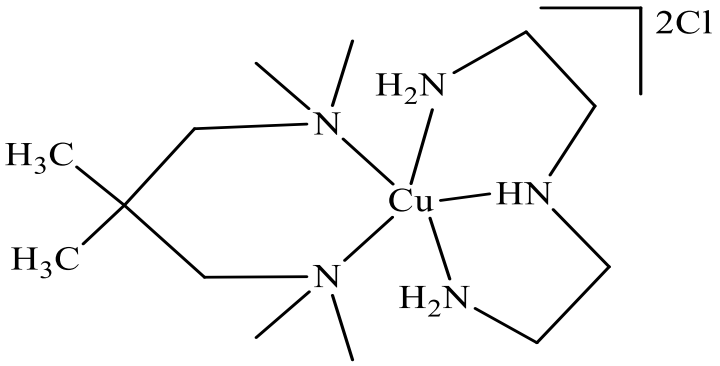
MS m/z 282.2 [M+] for $C_{10}H_{29}Br_2CuN_5$ Calculated: C, 27.13; H, 6.60; N, 15.82. Found C, 27.08; H, 6.54; N, 15.68%, IR (KBr, νcm^{-1}): 3375 (ν_{H2O}), 3350, 3272 and 3120, (ν_{H-N}), 2920 (ν_{C-H}), 1560 (ν_{N-H}), 1162 (ν_{N-C}), 515 (ν_{Cu-N}). UV–Vis.(in H_2O): λ_{max} (ε_{max} /M^{-1} cm^{-1}): 255 nm (1.30 x 10^3 M^{-1}L^{-1}) and 625 nm (3.10 x 10^2 M^{-1}L^{-1}); M.p. = 145 °C; Yield 85%.

Complex 8:



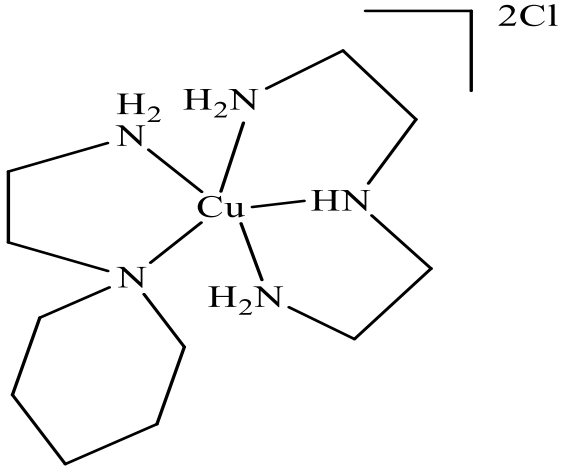
MS *m/z* 226.2 [M+] for $C_6H_{21}Cl_2CuN_5$ Calculated: C, 18.64; H, 5.47; N, 18.11. Found C, 18.41; H, 5.35; N, 18.09%, IR (KBr, νcm^{-1}): 3350 (ν_{H2O}), 3370 and 3268 and 3125 (ν_{H-N}), 2940 (ν_{C-H}), 1585 (ν_{N-H}), 1150 (ν_{N-C}), 520 (ν_{Cu-N}).UV–Vis.(in H_2O): λ_{max} (ε_{max} /M^{-1} cm^{-1}): 250 nm (1.50 x 10^3 M^{-1}L^{-1}) and 605 nm (2.80 x 10^2 M^{-1}L^{-1}); M.p. = 125 °C; Yield 90%.

Complex 9:



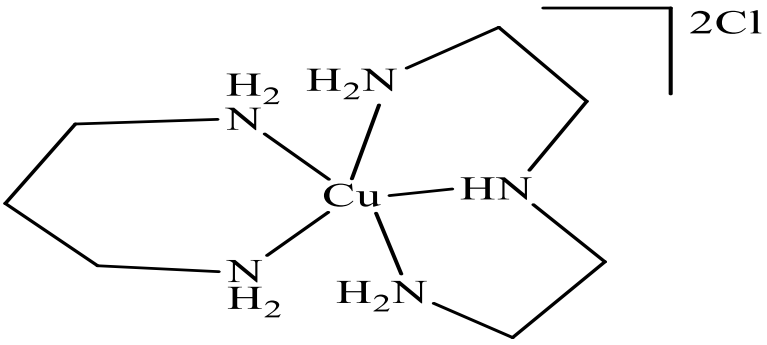
MS m/z: 324.22 for $C_{13}H_{35}Cl_2CuN_5$. Calculated: C, 32.21; H, 7.28; N, 14.45 . Found C, 20.41; H, 6.35; N, 16.09%, IR (KBr, νcm^{-1}): 3360 (ν_{H2O}), 3355 and 3260 and 3130 (ν_{H-N}), 2935 (ν_{C-H}), 1575 (ν_{N-H}), 1160 (ν_{N-C}), 517 (ν_{Cu-N}).UV–Vis.(in H_2O): λ_{max} (ε_{max} /M^{-1} cm^{-1}): 245 nm (1.40 x 10^3 $M^{-1}L^{-1}$) and 620 nm (2.95 x 10^2 $M^{-1}L^{-1}$); M.p. = 135 °C; Yield 70%.

Complex 10:



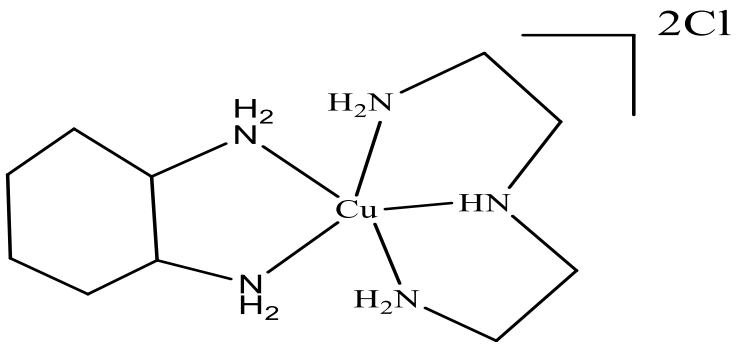
MS m/z: 294.17 for $C_{11}H_{29}Cl_2CuN_5$. Calculated: C, 29.05; H, 6.43; N, 15.40. Found C, 19.31; H, 5.95; N, 16.59%, IR (KBr, νcm^{-1}): 3355 (ν_{H2O}), 3340 and 3275 and 3140 (ν_{H-N}), 2945 (ν_{C-H}), 1580 (ν_{N-H}), 1154 (ν_{N-C}), 519 (ν_{Cu-N}).UV–Vis.(in H_2O): λ_{max} (ε_{max} /M^{-1} cm^{-1}): 253 nm (1.33 x 10^3 $M^{-1}L^{-1}$) and 615 nm (2.75 x 10^2 $M^{-1}L^{-1}$); M.p. = 140 °C; Yield 86%.

Complex 11:



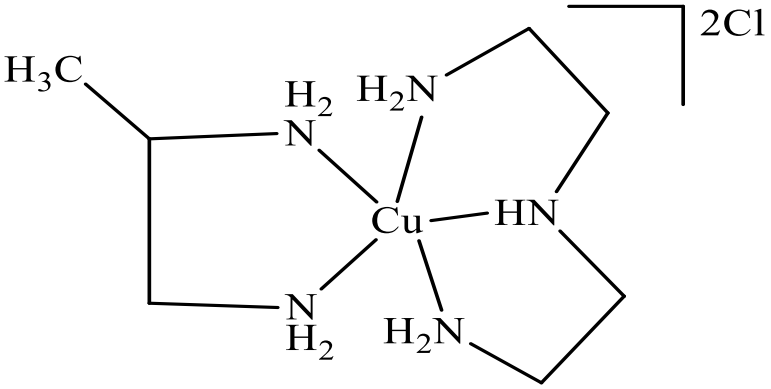
MS m/z: 240.12 for $C_7H_{23}Cl_2CuN_5$. Calculated: C, 20.98; H, 5.79; Br, 39.89; Cu, 15.86; N, 17.48. FoundC, 25.08; H, 6.50; N, 17.68%, IR (KBr, νcm^{-1}): 3366 (ν_{H2O}), 3360, 3250 and 3135, (ν_{H-N}), 2925 (ν_{C-H}), 1570 (ν_{N-H}), 1165 (ν_{N-C}), 525 (ν_{Cu-N}). UV–Vis.(in H_2O): λ_{max} (ε_{max} /M^{-1} cm^{-1}): 249 nm (1.25 x 10^3 $M^{-1}L^{-1}$) and 625 nm (3.10 x 10^2 $M^{-1}L^{-1}$); M.p. = 143 °C; Yield 87%.

Complex 12:



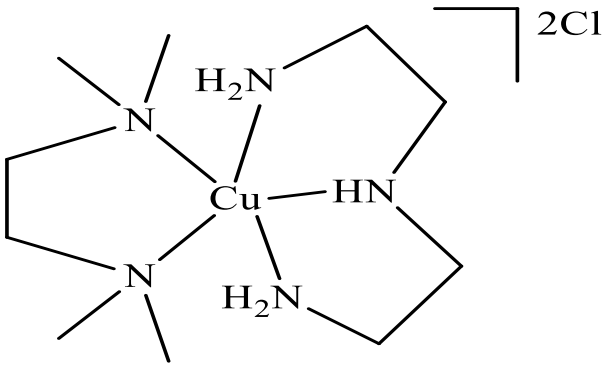
MS m/z: 252.13 for $C_8H_{23}Cl_2CuN_5$. Calculated: C, 23.28; H, 5.62; Br, 38.73; Cu, 15.40; N, 16.97. Found C, 22.55; H, 5.53; N, 18.78%, IR (KBr, νcm^{-1}): 3364 (ν_{H2O}), 3366, 3255 and 3145, (ν_{H-N}), 2930 (ν_{C-H}), 1565 (ν_{N-H}), 1152 (ν_{N-C}), 518 (ν_{Cu-N}). UV–Vis.(in H_2O): λ_{max} (ε_{max} /M^{-1} cm^{-1}): 257 nm (1.29 x 10^3 $M^{-1}L^{-1}$) and 611 nm (3.00 x 10^2 $M^{-1}L^{-1}$); M.p. = 153 °C; Yield 85%.

Complex 13:



MS m/z: 240.12 for $C_7H_{23}Cl_2CuN_5$ .Calculated: C, 20.98; H, 5.79; N, 17.48. Found C, 23.08; H, 5.54; N, 18.68%, IR (KBr, νcm^{-1}): 3354 (ν_{H2O}), 3366, 3255 and 3145, (ν_{H-N}), 2930 (ν_{C-H}), 1565 (ν_{N-H}), 1152 (ν_{N-C}), 518 (ν_{Cu-N}). UV–Vis.(in H_2O): λ_{max} (ε_{max} /M^{-1} cm^{-1}): 257 nm (1.29 x 10^3 M^{-1}L^{-1}) and 611 nm (3.00 x 10^2 M^{-1}L^{-1}); M.p. = 156 °C; Yield 77%.

Complex 14:



MS m/z 282.2 [M+] for $C_{10}H_{29}Cl_2CuN_5$ Calculated: C, 27.13; H, 6.60; N, 15.82. Found C, 27.08; H, 6.54; N, 15.68%, IR (KBr, νcm^{-1}): 3375 (ν_{H2O}), 3350, 3272 and 3120, (ν_{H-N}), 2920 (ν_{C-H}), 1560 (ν_{N-H}), 1162 (ν_{N-C}), 515 (ν_{Cu-N}). UV–Vis.(in H_2O): λ_{max} (ε_{max} /M^{-1} cm^{-1}): 255 nm (1.30 x 10^3 M^{-1}L^{-1}) and 625 nm (3.10 x 10^2 M^{-1}L^{-1}); M.p. = 145 °C; Yield 85%.

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Appendix

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ORIGINAL ARTICLE

Diethylenetriamine/diamines/copper (II) complexes $[Cu(dien)(NN)]Br_2$: Synthesis, solvatochromism, thermal, electrochemistry, single crystal, Hirshfeld surface analysis and antibacterial activity

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Cu(II) complexes;
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Abstract Two dicationic water soluble mixed triamine/diamine copper (II) complexes, of general formula $[Cu(dien)NN]Br_2$ **(1–2)** [dien = diethelenetriamine and NN is *en* = ethylenediamine or Me_4en = N,N′,N,N′-tetramethylethylenediamine] were prepared under ultrasonic mode with a relatively high yield. These complexes were characterized by elemental microanalysis, UV visible IR spectroscopy, and thermal and electrochemical techniques. In addition, complex **2** structure was solved by X-ray single crystal and Hirshfeld surface analysis. The complex exhibits a distorted square pyramidal coordination environment around Cu(II) centre. The solvatochromism of the desired complexes was investigated in water and other suitable organic solvents. The results show that the Guttmann's DN parameter values of the solvents have mainly contributed to the shift of the d–d absorption band towards the linear increase in the wavelength of the absorption maxima of the complexes. The complex **1** showed higher antibacterial activity against the studied

جامعة النجاح الوطنية
كلية الدراسات العليا

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فاطمة علي مصطفى ابو سليمة

إشراف
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قدمت هذه الأطروحة استكمالاً لمتطلبات الحصول على درجة الماجستير في الكيمياء، بكلية الدراسات العليا في جامعة النجاح الوطنية في نابلس، فلسطين
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الملخص

في هذه الدراسة تم تحضير معقدات النحاس ثلاثي/ثنائي الامين وذلك باضافة مركب ثنائي الامين ومركب اخر ثلاثي الامين بنفس الكمية والمقدار مع نفس المقادير من املاح بروميد النحاس او كلوريد النحاس تحت تأثير الموجات فوق الصوتية.

شخصت المعقدات المعزوله بواسطة العديد من القياسات الفيزيائيه مثل طيف الاشعه تحت الحمراء, طيف الامتصاص الفوق بنفسجي و الملون, التحليل العنصري, طيف الكتله, التحليل الحراري الوزني, التحليل الكهروكيميائي وحيود الاشعه السنيه البلوري.

احد المعقدات تم قياس البنيه الفراغيه حول الذرة المركزية وشخصت على انها هرم رباعي الاوجه مشوه.

تم اجراء تحليلات هيرشفيلد لسطح المعقد المقاس بواسطة اشعة اكس وحددت مناطق الاتصال بين الجزيئات ونسب الذرات المشاركه بها.

الظاهره اللونيه المرتبطه بالمذيبات تم تحديدها لاحدى المعقدات باستخدام العديد من المذيبات العضويه بالاضافة الى الماء, طبقت قاعدة جوتمان في الدراسه حيث اظهرت المعقدات ميول لاستقبال الالكترونات.

1- اظهرت معظم المعقدات نشاط عالي ضد انواع مختلفة من البكتيريا مثل

Staphylococcus aureus